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DEGREE FOR WHICH THESIS WAS PRESENTED.... Ph D.....

YEAR THIS DEGREE GRANTED..... 1974.....

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SOME APPROACHES TO THE SYNTHESIS OF THE CYATHINS

by

(C) SALVADOR FERNANDEZ

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

FALL, 1974

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

SOME APPROACHES TO THE
SYNTHESIS OF THE CYATHINS

submitted by SALVADOR FERNANDEZ in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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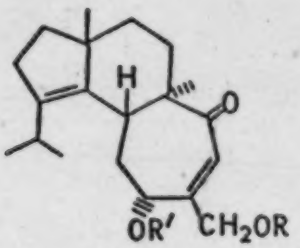
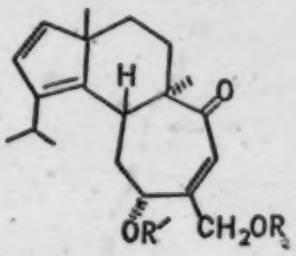
ABSTRACT

The cyathins are metabolites of the bird's nest fungus Cyathus helenae. They are members of a new family of diterpenoids which had not previously been characterized. Cyathin A_3 (1) and allocyathin B_3 (2) were the first members of this family whose structures were determined.

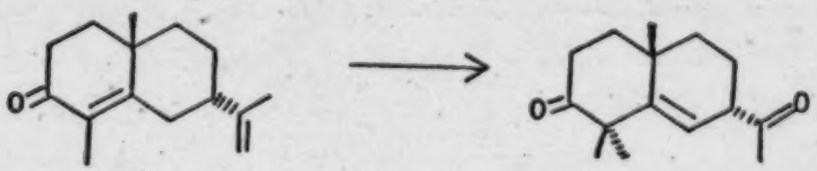




1 R, R′ = H

2 R, R′ = H

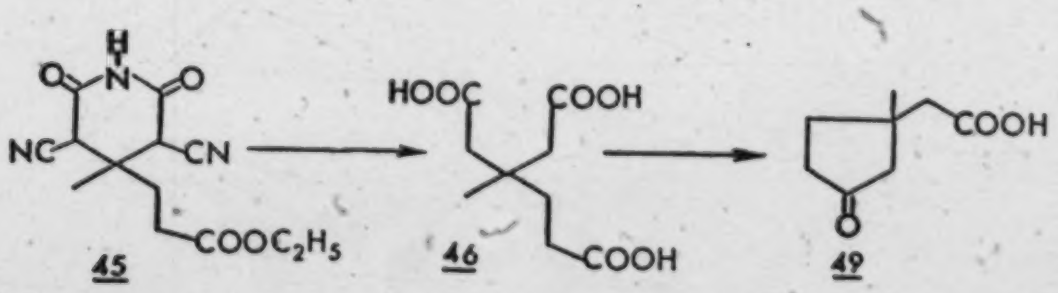
This thesis describes some approaches to the synthesis of the cyathin skeleton. The routes examined include the synthesis of the bicyclic compound 100 representing potential rings A and B



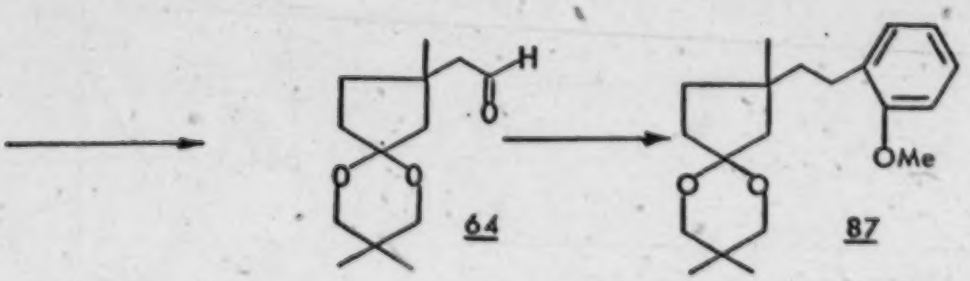
105 100

Another approach involves the construction of the diketone 91 and cyclization of 91 to the tricyclic ketol 94. Compound 91 was prepared in the following way. The triacid 46, obtained from the glutarimide 45, was converted to 49

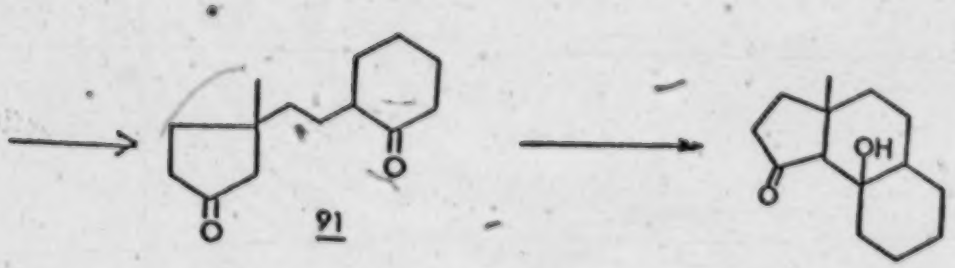
via a Dieckmann cyclization. The acid 49 was in turn transformed after esterification and protection of the carbonyl group into aldehyde 64. After Grignard reaction with o-iodoanisole followed by dehydroxylation compound 87 was obtained. The latter was converted to the diketone 91 by Birch reduction and hydrogenation. Ketol 94 was secured by the intramolecular aldol condensation of 91. The stereochemical aspects of this cyclization are discussed.



45 46 49



64 87



91 94

Some intramolecular Diels-Alder reactions involving a furan ring as the diene were also examined in an effort to produce a suitably functionalized ring C of the cyathins. For example, 22 spontaneously isomerized to 22a on standing at room temperature.

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TABLE OF CONTENTS

	Page
ABSTRACT	vi
ACKNOWLEDGEMENT	vii
LIST OF TABLES	ix
INTRODUCTION	1
I. APPROACHES TO THE CYATHANE SKELETON	
Discussion	18
A-C Approach	18
A-B Approach	66
Diels-Alder Approach	79
Conclusion	81
Experimental	85
Bibliography	137
II. AN INVESTIGATION OF SOME INTRAMOLECULAR DIELS-ALDER REACTIONS	
Discussion	147
Experimental	163
Bibliography	177

LIST OF TABLES

Table	Description	Page
Part I:		
1	Stereochemistry of the perhydrophenanthrenes. Order of stability.	19
2	Birch reduction of 2,6-dimethoxy-n-butylbenzene.	49
3	Modified Birch reduction of 2,6-dimethoxy-n-butylbenzene.	50
Part II:		
1	Intramolecular Diels-Alder reaction of furfurylamine derivatives	155
2	Intramolecular Diels-Alder reaction of furfuryl alcohol derivatives	156

INTRODUCTION

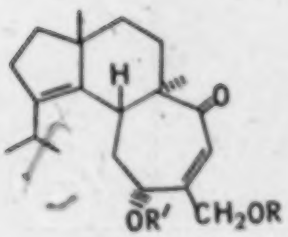
While on a field trip in the Rocky Mountains Dr. H.J. Brodie of the Botany Department of this University, purportedly as a consequence of a fall, discovered a new bird's nest fungus of the genus Cyathus[1]. This chance encounter led to other interesting findings. Brodie and co-workers were able to grow the fungus, designated Cyathus helenae, in liquid media[2]. They found that the culture broth inhibited the growth of bacteria that had contaminated the culture vessel. Extraction of the culture broth with ethyl acetate afforded a mixture that showed antibiotic activity. This mixture, or "cyathin complex" as it was designated, was then studied by Ayer and co-workers in an effort to isolate the active components[3].

One of the components of the mixture was sparingly soluble in chloroform and was separated by triturating the crude cyathin with chloroform. This constituent was shown to be 2,4,5-trihydroxybenzaldehyde. A combination of column chromatography and preparative thin layer chromatography of the cyathin complex afforded a material which appeared to be pure and which was called cyathin A_3. This material, however, was not crystalline and later was shown to be a mixture of two components. Since the two components differ in the degree of unsaturation, one being the dihydro derivative of the other,

they were separated by chromatography on silica gel impregnated with silver nitrate[4].

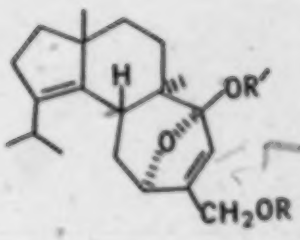
The structure determination work was carried out largely on the more abundant cyathin A_3. A thorough analysis of the chemical and spectroscopic properties of cyathin A_3 and allocyathin B_3 and their derivatives led Ayer and Taube[5] to propose structures 1 and 2 respectively for this substance. These deductions have been confirmed by an X-ray crystallographic study[6] of cyathin A_3 (which crystallizes in the hemiketal form 1a). This study also revealed the relative and absolute stereochemistry of cyathin A_3. Subsequent work by Ayer and Carstens has shown that cyathin B_3 and cyathin C_3, two further metabolites of C. helenae, have structures 3 and 4[7]. Cyathin A_3 and allocyathin B_3 exist partially as the internal hemiketals 1a and 2a respectively, a fact that complicated the initial work. On acetylation, 1 and 2 give the diacetyl derivatives 1b and 2b. Treatment of 1 and 2 with methanolic HCl leads to the formation of the internal methyl ketals 1c and 2c respectively.

The cyathins belong to a family of diterpenes hitherto unknown. Because of the novel skeleton present in these compounds we became involved in investigating possible routes for its construction. Since this thesis details initial exploratory work directed towards the synthesis of the cyathane ring system, the remainder of the Introduction will



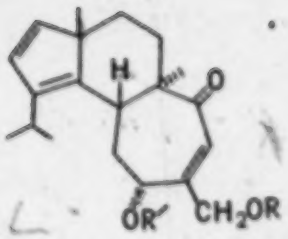
1 R, R′ = H

1b R, R′ = Ac



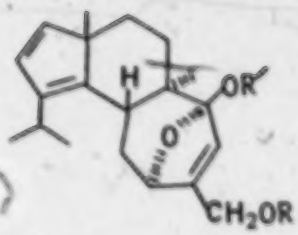
1a R, R′ = H

1c R = H, R′ = CH3



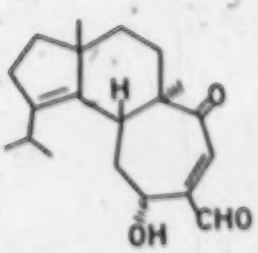
2 R, R′ = H

2b R, R′ = Ac



2a R, R′ = H

2c R = H, R′ = CH3



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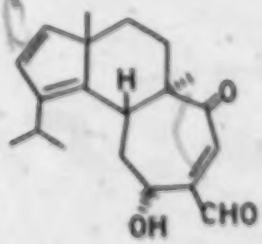
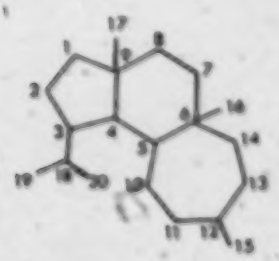
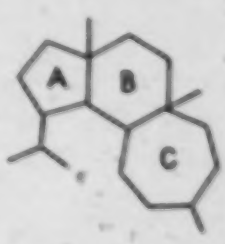


4

be devoted mainly to a discussion of some of the initial ideas behind the work described later. It is not intended to describe all conceivable routes to the cyathins. Such an undertaking would require much space and is, of course, restricted by our own prejudices and lack of imagination and knowledge. Brief reviews are available on total synthesis of diterpenes[8] and a recent review on the synthesis of the hydroazulenes[9] may also be useful to visualize some of the alternatives that we faced at the outset of this work.

In order to analyze some of the possible synthons and evaluate routes to their construction let us examine first the cyathane skeleton. The numbering follows a modified steroidal numbering system. The rings are designated A, B, and C as shown.

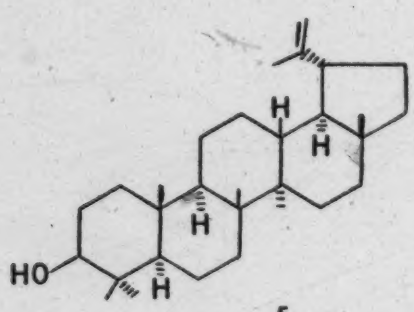




Any synthesis of the skeleton must take into consideration the existing dissymmetric centres. Of the possible six dissymmetric centres of the cyathane ring system (carbons 3, 4, 5, 6, 9 and 12) in the cyathins thus far reported, only three dissymmetric carbons are present. Of

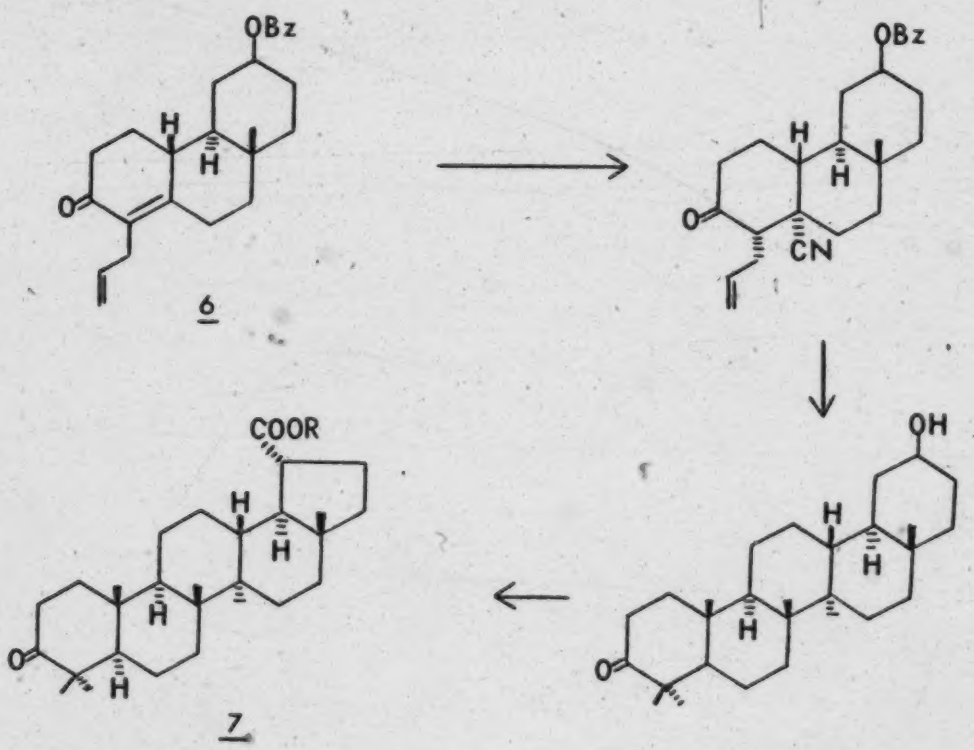
these four, the more difficult problem would appear to be that of building the dissymmetric carbons at the ring junctions (5,6,9) in the proper orientation. The stereochemistry at carbon 11, while important, should not be as demanding. Carbon 11 owes its dissymmetry to the presence of an alcohol group and thus should be controllable through the corresponding ketone. Thus the first task is that of synthesizing a tricyclic five-six-seven-membered ring system containing three dissymmetric carbons at the ring junctions.

Needless to say there are a great number of synthons that may be envisioned as leading to the cyathane skeleton. One may attempt to build the tricyclic system with the rings already of the right size or construct it in such a way that ring expansion, ring contraction or both would produce the desired ring arrangement. Let us consider the synthesis of lupeol 5 by Stork[10]. It is relevant since rings C, D and E are similar to those of cyathin A_3 having the same stereochemical arrangement.



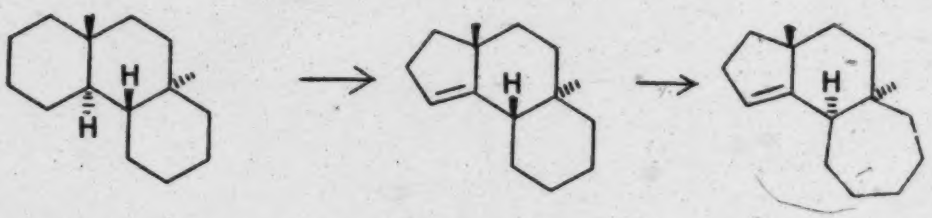
5

The ketone 6 gave, after treatment with diethylaluminum cyanide, the trans-anti-trans-cyanoketone. The cyano group was converted to a methyl group in subsequent stages. Ring E originally present as a six-membered ring was modified at the end of the synthesis and converted, by oxidation of the alcohol to the ketone, ozonolysis of the corresponding enol acetate and cyclization of the modified ozonolysis product, to a five-membered ring in 7.



The key step, 1,4 addition of cyanide, leaves a ketone group in the "wrong" position as far as the synthesis

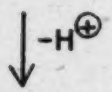
of cyathin A_3 is concerned. The lupeol synthesis, however, exemplifies the possibility of modifying an existing six-membered ring into a suitable five-membered ring. Bearing this in mind and also the possibility of expansion of ring C one may consider the initial synthesis of a properly substituted six-six-six framework such as 8 and modify it at a later stage.

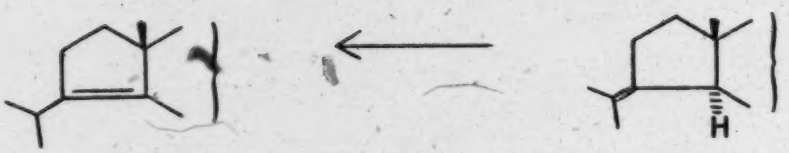


8 9 10

This scheme is attractive since 8 possesses a trans-anti-trans arrangement of the ring junctions. Such an arrangement is the most stable thermodynamically[11] and should be relatively straightforward to secure. For the ring contraction step, i.e., 8 to 9, one can envision the use of the acid catalyzed rearrangement of ring A of triterpenoids[12]. Loss of the hydroxyl group in 11 takes place with migration of the C_4-C_5 bond to give 12, elimination of a proton yields the isopropylidene 13 and double bond migration produces 14. This latter product possesses a contracted ring A identical with the one present in cyathin A_3.

11 12





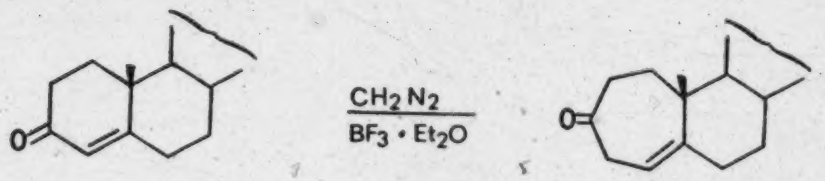
14 13

It is known that diazo compounds add to cyclic ketones to give the ring expanded ketone[13]. Kohler and co-workers[14], for example, report the treatment of cyclohexanone with diazomethane, generated in situ, to obtain a mixture of cycloheptanone and methylenecyclohexane oxide.

63% 15%

The addition to α,β-unsaturated ketones also takes place with ring enlargement. Johnson and co-workers[15] have homologated steroidal α,β-unsaturated ketones. Treatment of

cholestenone 15 with diazomethane and boron trifluoride etherate gives A-homo-cholestenone 16 in 40% yield.



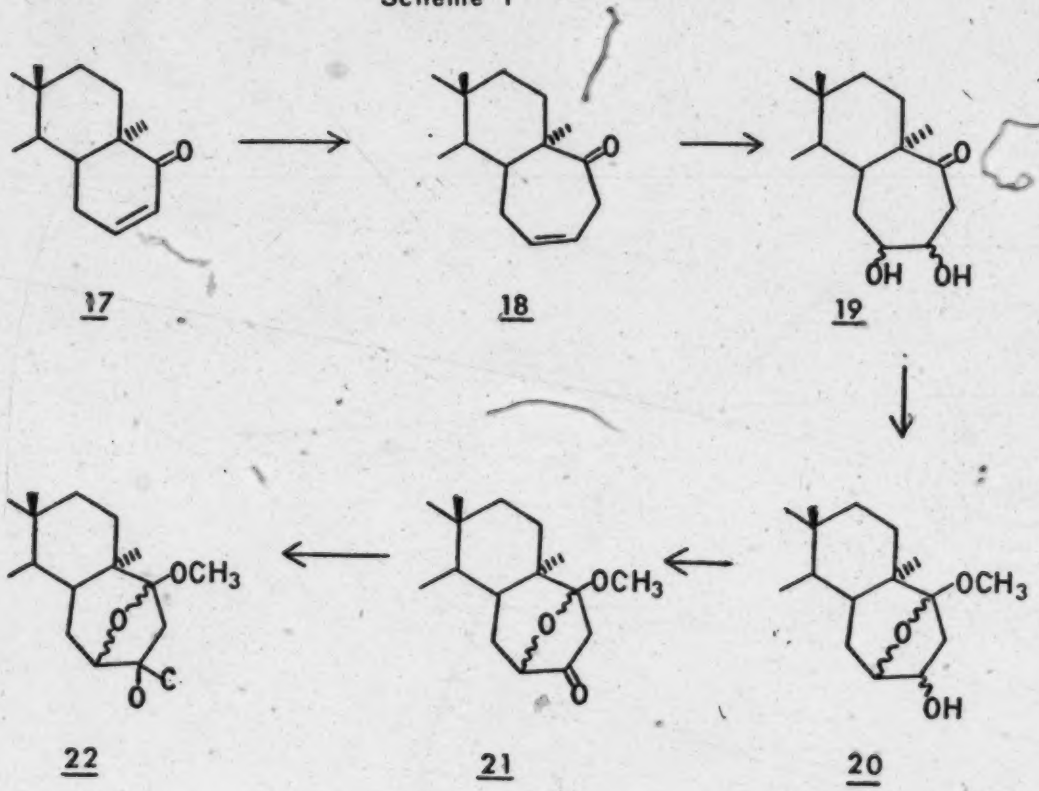
15 16

The same type of approach can be envisioned as a route to ring C of cyathin A_3.

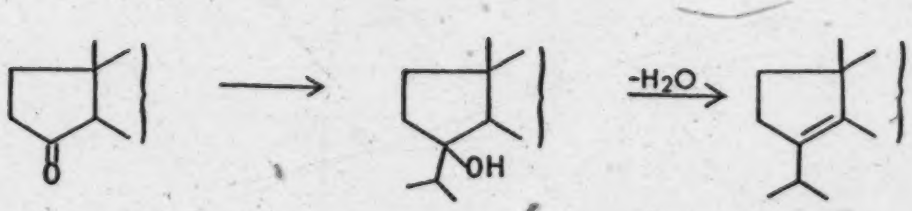
Preparation of a compound with a partial structure as in 17 and ring enlargement as previously described would yield 18. The double bond could then be hydroxylated to the dihydroxy compound 19. The latter would likely, as in cyathin A_3 and in the diol from 16, form an internal ketal, 20. This latter compound on oxidation would produce the ketone 21. Elaboration of 21 with an additional one carbon unit would complete the skeleton to give 22.

Other possibilities include the construction of a skeleton with a five-membered ring A. A suitable functional group at C-3 would allow the introduction of the isopropyl group. For instance, Grignard addition to a ketone such as 23, followed by dehydration of the alcohol leads to the properly substituted A ring 24.

Scheme 1



17 18 19 20 21 22



23 24

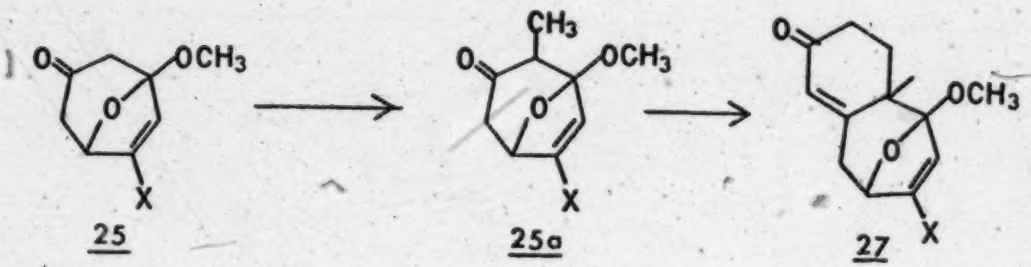
While the schemes may be feasible, the problem of synthesizing the tricyclic compound must first be surmounted. One approach is that of building one ring at a time. Any of the three rings could be the starting point. However, rings A and C seem the more logical starting points since they are the more functionalized. In this respect ring C as the first building block should be considered first.

The formation of the internal methyl ketal 1c by cyathin A_3 suggests a possible initial target, namely a cycloheptanone such as 25 or 26. Robinson annelation on 25a should lead to 27 that could then possibly be modified to form ring A. Similarly 26 could be converted to 29 by a Michael type addition on 28 followed by an aldol cyclization.

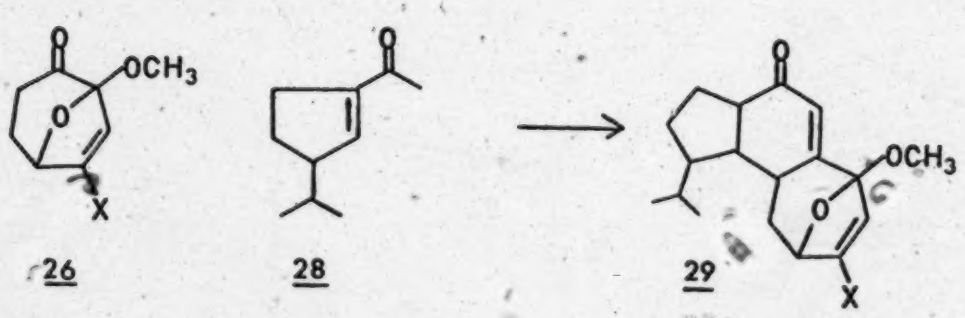
Synthesis of 25 and 26 can be envisaged as arising from ring expansion of a Diels-Alder adduct of 2-methoxyfuran. For instance, addition of 2-acetoxyacrylonitrile leads to the formation of 6-acetoxy-6-cyano-1-methoxy-7-oxabicyclo[2.2.1]-hept-2-ene 30[16]. Modification of the cyano group into an amine and this in turn into a diazo compound 31 would produce a good leaving group that could undergo elimination as indicated to produce 26.

On the other hand 30 could be converted to the ketone 32. Treatment with diazomethane should then produce 25 or 26.

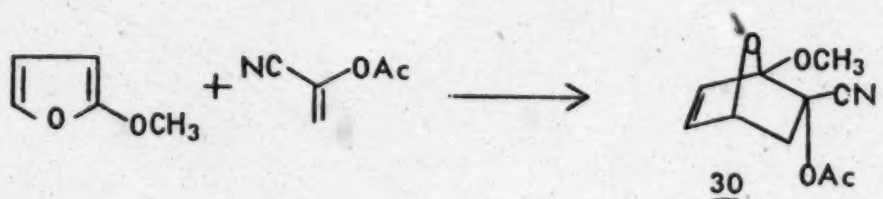
Scheme 2



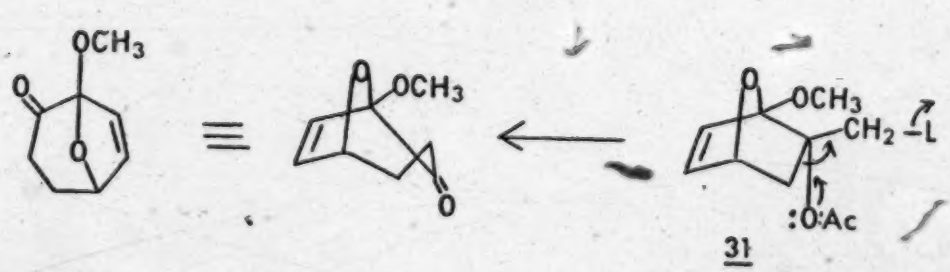
25 25a 27



26 28 29



30



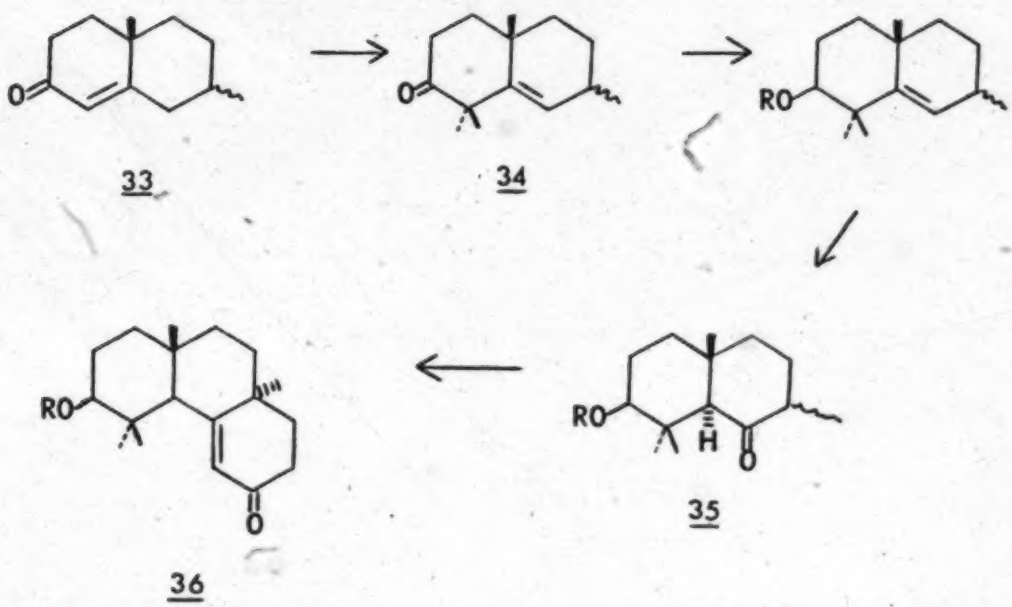
31

32

Another approach would be that of modifying a readily accessible bicyclic system. This could minimize the number of steps involved and give a more efficient synthesis. The two rings can be A-B, B-C or A-C. The possible combinations increase if one takes into account that ring A can be a six- or a five-membered ring and ring C a six- or seven-membered ring. Briefly described in the following schemes are examples of some of the possible combinations.

In scheme 3, the starting block is the ketone 33. It can be readily prepared by a Robinson annelation of methyl vinyl ketone and 2,5-dimethylcyclohexanone. Methylation may lead to the dimethylated β,δ-unsaturated ketone 34, and this can be oxidized, following reduction of the C-3 carbonyl and protection of the alcohol, to the ketone 35. The last compound could undergo another Robinson annelation to produce 36.

Scheme 3

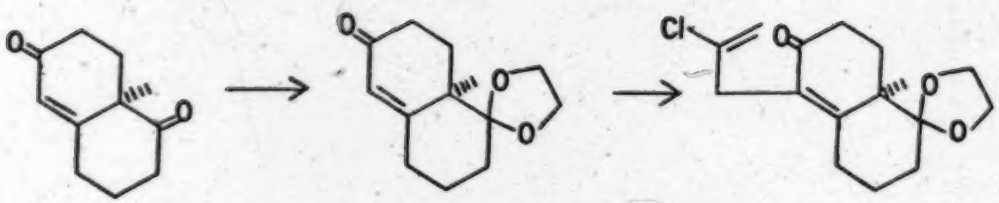


33 34 35 36

The readily accessible Wieland-Miescher ketone (scheme 4) can be monoalkylated with 2,3-dichloropropene to 37. Addition of methyl lithium leads to the allylic alcohol 38[17] which could potentially be cyclized by acid treatment to 39, this last step being patterned after the work of Lansbury[18].

If a compound such as 40 (scheme 5) could be prepared, it should undergo an aldol cyclization to produce the tricyclic diketone 41.

Scheme 4



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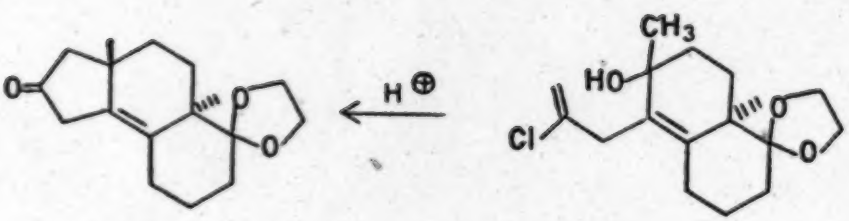
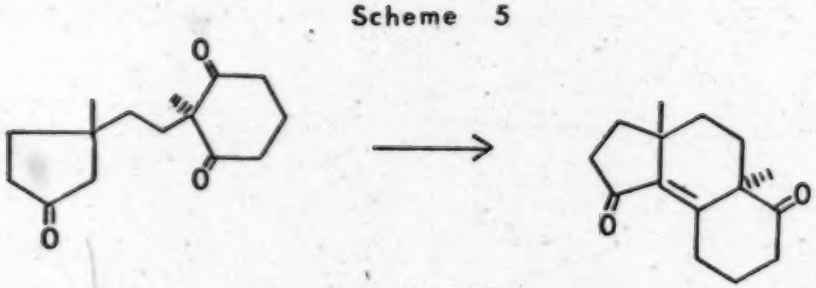


39 38

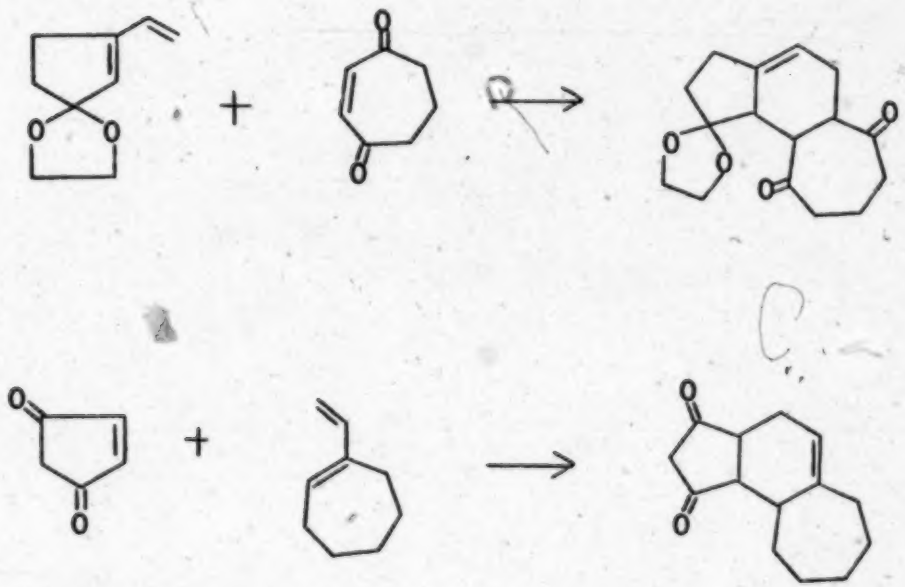
Scheme 5



40 41

Lastly, the tremendous synthetic potential of the Diels-Alder reaction might be employed (as exemplified on scheme 6), using rings A and C as diene or dienophile respectively.

Scheme 6



It is the purpose of this thesis to present the initial studies on some of these possibilities, to evaluate their synthetic utility and scope and to provide potentially useful modifications in order to increase their utility. The work is divided into two parts. The first part describes the

work done towards the two ring approach, namely, formation of modified rings A-B and A-C. The second part describes our attempts to generate a properly substituted C ring.

Part I : APPROACHES TO THE CYATHANE SKELETON

DISCUSSION

This section deals with three different approaches to a tricyclic synthon for cyathin A_3. Schemes 3, 5 and 6 outline the initial plans. The results will be discussed separately under the headings: A-C approach, A-B approach and Diels-Alder approach.

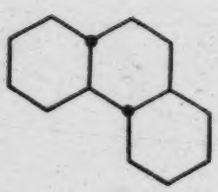
A-C Approach

The rationale for the construction of a system such as 40 stems from our assumption that the most difficult task in the skeletal construction would be that of introducing the methyl groups at the ring junctions in the correct orientation. We considered that if 40 were to cyclize, it would do so giving rise to a mixture of the thermodynamically more stable stereoisomers, and that the stability of such a system would be reasonably similar to that of the perhydrophenantrenes. The order of stability of this latter system is well known[11]. It is summarized in the next table, the numbers indicating the order of stability.

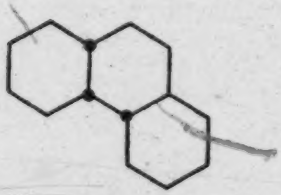
Inspection of the four more stable isomers shows that only one, the cis-anti-trans isomer, has the extreme asymmetric centres in a cis relationship. Thus the probability of securing a trans relationship of the methyl groups seemed reasonably high. While the number of possible

stereoisomers which could be formed by cyclization is relatively large, two of the dissymmetric centres would be removed on dehydration of the derived ketol. This should give rise to a mixture of only two stereoisomers one of which, the trans isomer, should predominate.

Table 1



1



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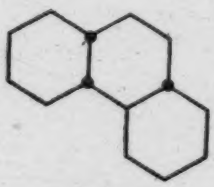

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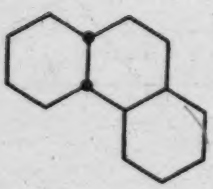

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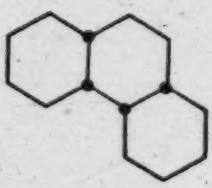

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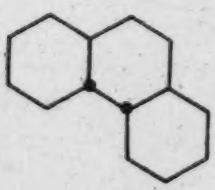
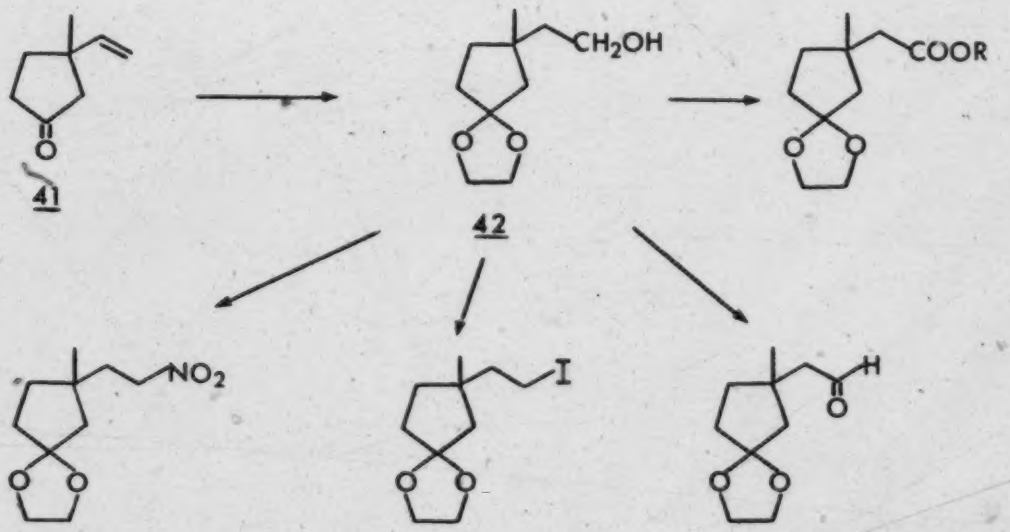


5

Our initial concern was that of synthesizing the appropriate 3,3-disubstituted cyclopentanone. One of the substituents had to be a methyl group while the second substituent should be a two carbon substituent such that it could be easily modified to enable more than one mode of coupling of the terminal carbon. With these considerations in mind we attempted to prepare 3-methyl-3-vinylcyclo-

pentanone 41. The vinylic group could, after protection of the carbonyl, be transformed by hydroboration to the primary alcohol 42. The hydroxyl group could then be modified in such a way as to render the carbon either electrophilic or nucleophilic.



It has been shown by Hooz and Layton[19] that 1,4 addition of a vinyl group to α,β-unsaturated ketones can be achieved by the use of a divinylcopper lithium tri-n-butylphosphine complex. Later Corey and Beames[20] reported the use of a mixed cuprate reagent of the type R_1R_2CuLi to achieve a similar reaction. The use of the divinylcopper lithium reagent on the readily accessible 3-methyl-2-cyclopentenone[21] led to a mixture that contained a cyclopentanone, ir 1745 cm^{-1}. Our attempts to isolate the compound, however, met with failure and the approach

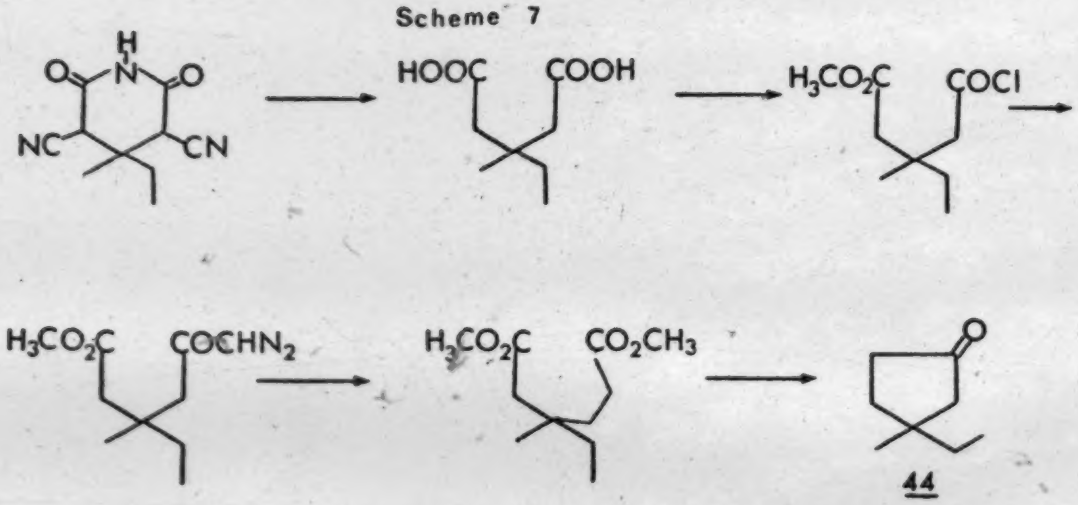
was abandoned. More recently a simplified work-up procedure has been developed[22] which may facilitate the isolation of 41. This has not been investigated.

Lansbury and co-workers[23] in their approach to the synthesis of hirsutic acid used 3-carbomethoxy-3-methyl-cyclopentanone 43 as their starting material. The cyclopentanone had been prepared previously[24] by a simple and efficient route. At first we considered the use of such a compound directly. The idea, however, was not pursued since we thought that the carboxyl derived reactive site might prove too hindered (neopentyl type system).

The simpler 3,3-dialkylcyclopentanones have been prepared. The synthesis of 3,3-dimethylcyclopentanone[25] is inefficient and cannot be easily modified to prepare a suitably substituted cyclopentanone. The construction of 3-methyl-3-ethylcyclopentanone 44[26], scheme 7, while laborious, brought to our attention the potential use of the Guareschi reaction[27]. When ethyl cyanoacetate reacts with ketones (methyl ketones give the best results) in the presence of ammonia, an α,α'-dicyano-β,β-disubstituted glutarimide is formed. Hydrolysis leads to the β,β-disubstituted glutaric acids.

The preparation of 44 necessitates an homologation step. This need could be bypassed if one were to use a levulinic acid ester. Since the acid produced on hydrolysis

Scheme 7



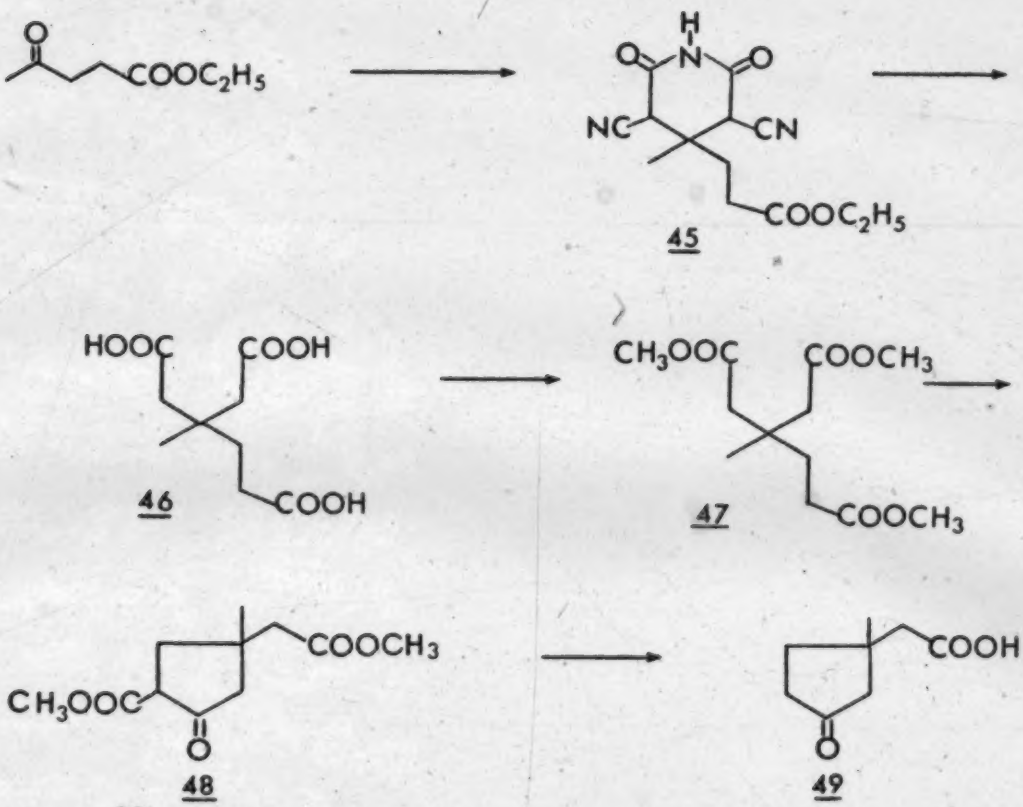
44

of the glutarimide would be both a glutaric and an adipic acid, cyclization to the required cyclopentanone could be carried out without further lengthy modification.

The synthesis of the desired 1-methyl-3-oxocyclopentaneacetic acid 49 was achieved as shown in Scheme 8.

In 1960, Handly, Nelson and Somers[28] reported the synthesis of a number of glutaric acids via the Guareschi reaction. Their procedure was followed using ethyl levulinate[32] as the ketone. The yields of α,α'-dicyano-β-methyl-β-(ethoxycarbonylethyl)glutarimide 45, were usually around 50% although yields as high 63% and as low as 40% were obtained on occasion. Later we found that 45 had been prepared

Scheme 8



previously[29] although neither experimental detail nor yield is reported. No further attempts to increase the yield were made. Potentially a two step procedure might be employed to secure better yields. Treatment of diethyl 2-cyano-3-methyl-hex-2-enedioate (from the Knoevenagel reaction of ethyl cyano-acetate and ethyl levulinate)[30] with cyanoacetamide and sodium ethoxide should produce the starting glutarimide 45[31].

While the preparation of the imide could be carried out without difficulty, the hydrolysis to the triacid 46 proved troublesome. The reported conditions for hydrolysis[26,28,30] as well as a number of variations using sulfuric

and/or phosphoric acid at different concentrations, temperature and time led, in the best of cases, to only fair yields of 3-methyl-3-carboxymethyladipic acid 46. Furthermore, the results were not reproducible. Attempts to hydrolyse the imide under basic conditions, 10% potassium hydroxide in ethylene glycol at 180°, led to extensive decomposition of the starting material. Finally, acid hydrolysis employing concentrated hydrochloric acid at reflux temperature for 14 hours led to a 60% yield of 46. Four days of reflux under these conditions increased the yield to 74%. The yield of isolated product was further increased by continuous extraction of the reaction mixture with ether. In this manner yields of over 90% may be obtained reproducibly in mole-scale preparations. The crude acid mp 142 - 146° (lit.[29] 149°) was used in the following step without purification.

The conversion of the triacid to dimethyl 3-methyl-3-methoxycarbonylmethyladipate 47, was attempted in several ways. Klostergaard's esterification method[32], successfully used for the preparation of ethyl levulinate, afforded only a 25% yield of crude 47. Direct Fischer esterification using methanol and sulfuric acid gave only a 45% yield of impure triester. Seemingly, the triester decomposes under these conditions. Later we learned that 47 is prone to decomposition when heated. Milder esterification conditions were explored. 2,2-Dimethoxypropane has been used successfully as a water-scavenger in esterification reactions[33]. It is

reported that very mild conditions are required to effect the reaction. In our hands, however, no ester formation could be detected even after prolonged periods of time.

The use of "the catalytic dehydrator" described by Vesley and Stenberg[34], a combination of an acid polymer and a dehydrating agent, gave excellent yields of the ester in very pure form. The method is very efficient and quite mild. In practice the acid is dissolved in the alcohol required to form the ester, then to the solution a 7:3 mixture of anhydrous calcium sulphate and Rexyn 101(H) R-204 is added and the resulting slurry is stirred at room temperature until esterification is complete. Filtration of the catalyst followed by removal of solvent and percolation through silica gel gave yields of over 85%.

The Dieckmann cyclization of 47 to methyl 4-methoxycarbonyl-1-methyl-3-oxocyclopentaneacetate 48 did not take place when the triester was heated with sodium methoxide in refluxing toluene. Only starting material was recovered after work-up. The same negative result was obtained using sodium metal in refluxing benzene. Treatment of the triester with sodium and a catalytic amount of methanol in refluxing xylene, however, led to complete disappearance of the starting material in five hours. Work-up yielded a mixture of isomers of 48 in approximately a 1:1 ratio (by integration of the quaternary methyl singlets at δ 1.3 and 1.15 respectively).

The development of an intense blue color after treatment of 48 with ferric chloride was taken as an indication of the presence of a α-carbomethoxy ketone.

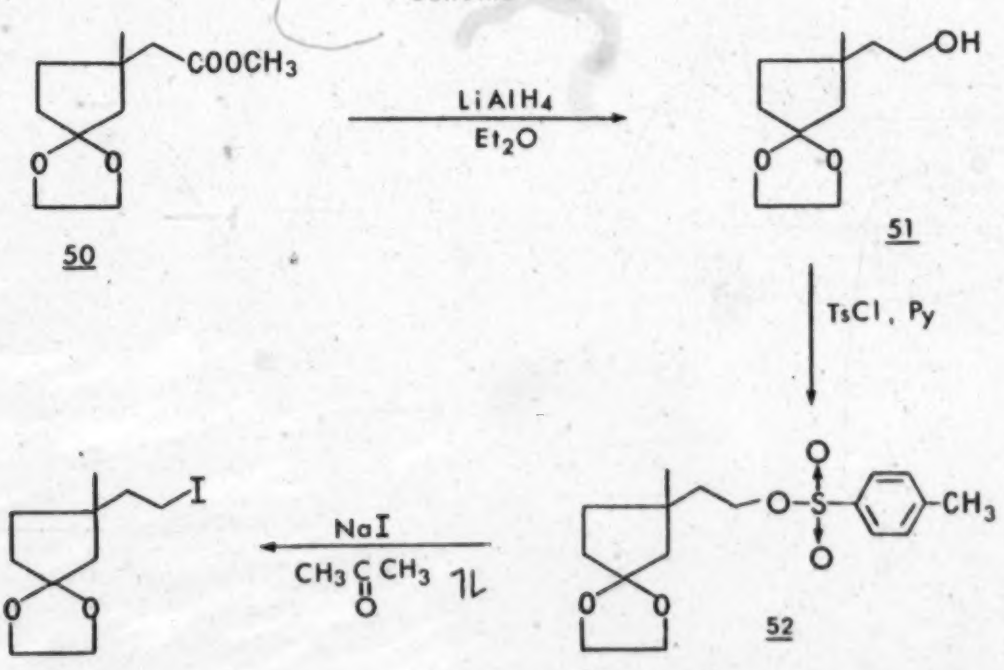
Hydrolysis and decarboxylation to 1-methyl-3-oxocyclopentaneacetic acid 49 was accomplished by heating 48 under reflux for 18 hours in 10% HCl. The hydrolysis of crude 48 proceeds satisfactorily. Thus a 90 - 92% yield of 49 is obtained from the triester 47 if purification of 48 is bypassed. The acid otained by this procedure was essentially pure and did not require further purification.

The esterification of 49 to methyl 1-methyl-3-oxocyclopentaneacetate 49a was carried out using the catalytic dehydrator as described earlier. The yields obtained were consistently high (>85%). Purification of this substrate, as before, was achieved by percolation through silica gel.

Having developed an efficient synthesis of methyl 1-methyl-3-oxocyclopentaneacetate 49a we then explored possible ways of coupling it to 2-methyl-1,3-cyclohexanedione or another suitable precursor. In order to study the alkylation, 49a was converted (see scheme 9) to 7-methyl-7-(2-iodoethyl)-1,4-dioxaspiro[4.4]nonane 53. Conversion of the ketone 49a to its ethylene acetal 50 was accomplished in quantitative yield by the conventional method. Reduction of the ester to 7-methyl-1,4-dioxaspiro[4.4]nonane-7-ethanol 51 was achieved by treatment of 50 with lithium aluminum

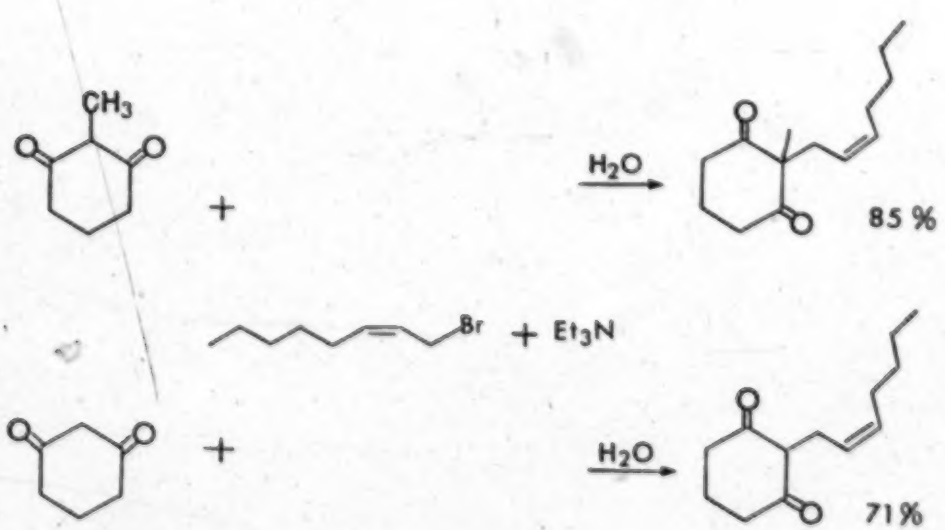
hydride in ether (90%). The alcohol was converted without purification to its p-toluenesulphonate 52 by treatment with p-toluenesulphonyl chloride in dry pyridine. The p-toluenesulphonate, a thick oil, was purified by washing with Skellysolve B at -70° (96%). However, none of our attempts to crystallize 52 were successful. Treatment of the tosylate with an excess of sodium iodide in refluxing acetone[35] afforded a 94% yield of the desired ketal iodide 53.

Scheme 9

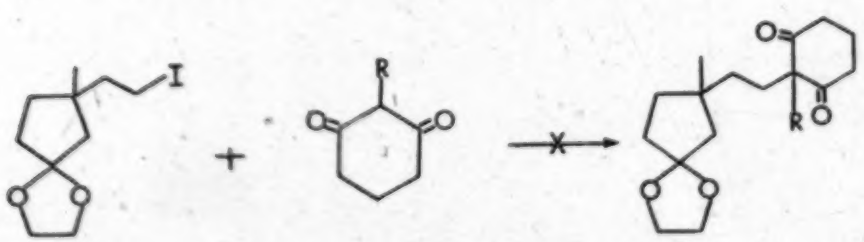


With 53 in hand, we turned our attention to finding a method to effect alkylation of 2-methyl-1,3-cyclohexanedione. An extensive discussion on alkylation appears in House's "Modern Synthetic Reactions" chapter 9[36]. Several reviews on alkylation of ambident anions are also available[37]. The diversity of reaction conditions and results reported tend to

make an understanding of the reaction, at best, difficult. Moreover, a discouraging fact seems to be clear. The alkylation of 1,3-dicarbonyl compounds is complicated by the formation of mixtures arising from C- and O-alkylation. Stetter and Dierichs studied the effect of solvent, concentration, metal cation, and leaving group in the alkylation of 1,3-cyclohexanedione.[38]. They found that more concentrated solutions led to higher ratios of C/O alkylation. They also found that higher yields of C-alkylation are obtained when using n-butyliodide (28.4%) as compared to n-butylbromide (18.2%). In our first attempts at alkylating 2-methyl-1,3-cyclohexanedione we used the conditions reported by these authors. Our compound, however, was recovered unchanged when we used their optimum conditions. Polgar and co-workers[39] have been able to achieve the following alkylations.



Their success could be partially ascribed to the fact that they were using allyl halides, one of the few substrates that lead to high C-alkylation yields[40]. One could also argue that some reaction between triethylamine and the allyl halide takes place to produce a tetraalkyl ammonium salt which in turn enhances the rate of the reaction. These compounds have been used as phase-transfer catalysts to promote otherwise difficult reactions[41]. In our hands no reaction could be observed between 1,3-cyclohexanedione or 2-methyl-1,3-cyclohexanedione and 53 using Polgar's conditions. The addition of equimolar amounts of triethylbenzylammonium bromide did not seem to have any effect. No reaction could be observed even after prolonged periods of time.



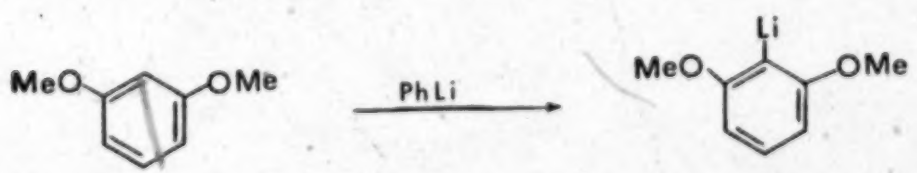
R = H, CH_3

Taylor and McKillop have reported that thallium (I) salts of 1,3-dicarbonyl compounds when treated with alkyl iodides give regiospecific C-alkylation in virtually quantitative yield[42]. This method was not attempted in view of the results obtained by Pizzorno and Albonico[43]. These workers found that thallium (I) salts of dimedone and 1,3-cyclohexanedione when treated with ethyl iodide produce

exclusively the O-alkylated compounds. Also, Hooz and Smith[44] found that thallium salts, contrary to Taylor and McKillop's claim, produced mixtures of C-, O- and C-dialkylated compounds, showing that they offer no synthetic advantage for promoting exclusive C-alkylation. At this stage this approach was discontinued.

Since we were not able to use the ketal-iodide 53 in the alkylation of 1,3-cyclohexanedione or 2-methyl-1,3-cyclohexanedione a different coupling method was sought. Also, we decided to use a compound that might be converted at a later stage to the desired dione.

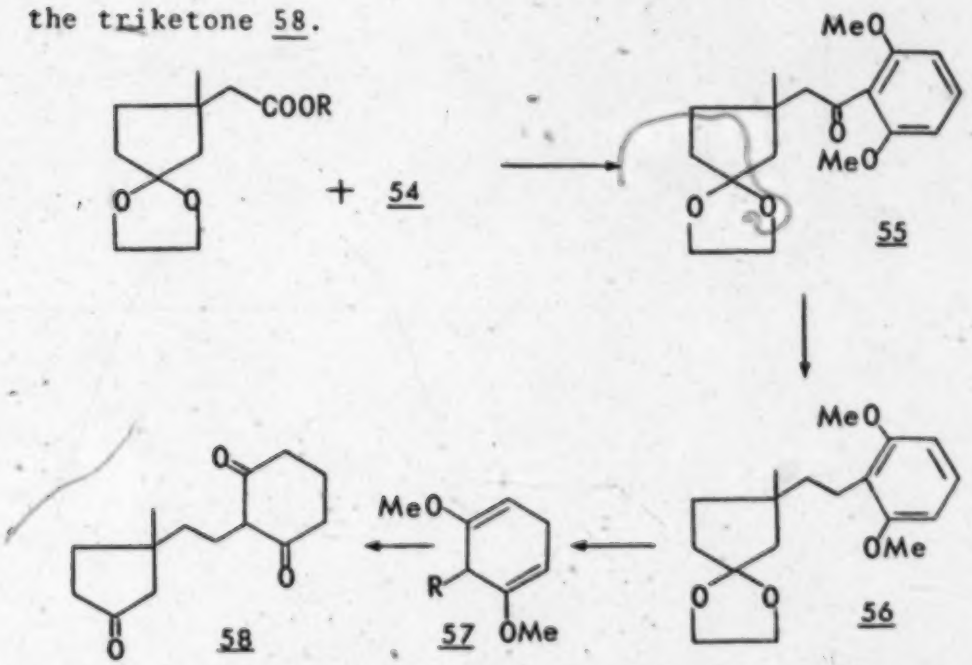
It is known[45] that some alkyl- and aryllithium compounds trans-metalate in the presence of aryl ethers giving rise to the ortho-lithiated aryl ether. In this fashion m-dimethoxybenzene metalates exclusively between the methoxy groups to afford 2,6-dimethoxylithiobenzene 54 when treated with phenyllithium[46].



54

Our initial intention was to react 54 with a protected cyclopentanone ester such as 50 in order to obtain the ketone 55. The ketone in turn could be removed by

suitable reduction. The substituted 2,6-dimethoxybenzene thus produced could then be reduced to the vinyl ether 57 by Birch reduction. Acid hydrolysis should then produce the triketone 58.



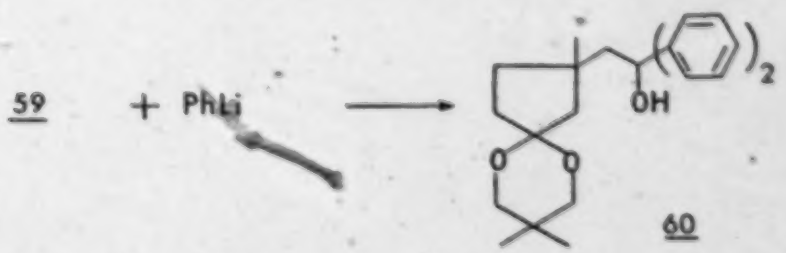
Bearing in mind that we wanted to use an aryllithium, a protecting group different from the ethylene acetal was prepared. This precaution was taken in view of the results obtained by Heathcock, Ellis and Badger[47]. These authors report that the ethylene ketals of cyclopentanone and cyclohexanone are attacked by isopropyl- and t-butyllithium. The products obtained are the alcohols formed by attack of the organolithium on the ketone liberated by E_2 elimination on the acetal.

These authors report that the 1,3-propyleneketal is stable under the same reaction conditions.

32

Ketalization of methyl 1-methyl-3-oxocyclopentane-acetate using 2,2-dimethyl-1,3-propanediol gave an 87% yield of the corresponding ketal 59 after chromatography on alumina.

When the ester 59 was treated with phenyllithium, the crystalline carbinol 60 was obtained in over 90% yield. We had expected that the intermediate ketone might be sufficiently hindered to avoid attack by a second molecule of phenyllithium. This proved not to be the case.



We speculated that perhaps by treating 59 with 2,6-dimethoxylithiobenzene in a 1:1 ratio, the reduced [illegible]ryllithium together with the added hindrance of the methoxyl groups flanking the reactive site might prevent further reaction with the ketonic intermediate. Thus when 54 (generated by treatment of m-dimethoxybenzene with n-butyllithium for 48 hours at room temperature) was allowed to react with the ester 59, a complex mixture of compounds was obtained. The ir spectrum of the mixture showed no carbonyl absorption but broad hydroxyl absorption at 3400 cm^{-1}. No attempts to separate the components of the mixture were made.

Amides react with organolithium compounds to form ketones[48]. Recently Owsley and co-workers[49] reported the preparation of 1,4- and 1,5-diketones by this approach. Also Scilly has reported the preparation of aldehydes and ketones by an in situ reaction of organolithium compounds with carboxamides[50].

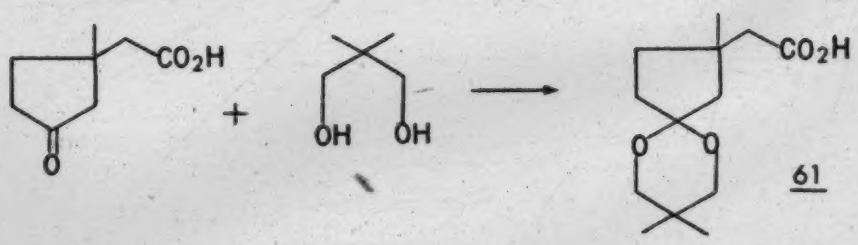
Lambooy has used 2,6-dimethoxylithiobenzene in the preparation of 2,6-dimethoxybenzaldehyde[51]. The aldehyde was obtained in 65% yield after treating N-methylformanilide with the aryllithium.

Attempting to take advantage of this method we explored methods of preparing an amide of 1-methyl-3-oxocyclopentaneacetic acid. Discouragingly, the methods

employed gave low yields of mixtures. For example, treatment of 49 with thionyl chloride in CH_2Cl_2-Et_3N followed by addition of N-ethylaniline afforded a 53% yield of a mixture containing the desired amide as the major compound. Ir: 1745 cm^{-1}, cyclopentanone, 1660 cm^{-1}, amide. nmr: δ 1.16 (tertiary CH_3), 1.12 (triplet, ethyl CH_3), 2.43 (singlet, CH_2CON), 3.75 (q., ethyl CH_2).

Mixtures were also obtained using oxalyl chloride or triphenylphosphine-carbon tetrachloride complex[52]. We felt that perhaps the poor results were due to the presence of the reactive ketonic carbonyl group. In order to circumvent this we prepared the 2,2-dimethyl-1,3-propanediol acetal of 1-methyl-3-oxocyclopentaneacetic acid 61. Using the usual ketalization conditions on 49, a mixture of compounds was obtained. The desired ketal-acid 61 was isolated in 45% yield by acid-base extraction of the mixture. Disappointingly this compound proved to be of no practical value since low yields of mixtures were obtained in our attempts at forming the corresponding amide (DCC, Et_2NH in CH_2Cl_2; N,N'-carbonyldiimidazole, Et_2NH). Treatment with thionyl chloride produced the acyl chloride, an unstable dark oil that resinified on standing. This approach was not further pursued.

The reaction of carboxylic acids with alkyl- or aryllithium compounds to produce ketones is a widely used procedure[53]. This method precludes, in most of the cases,

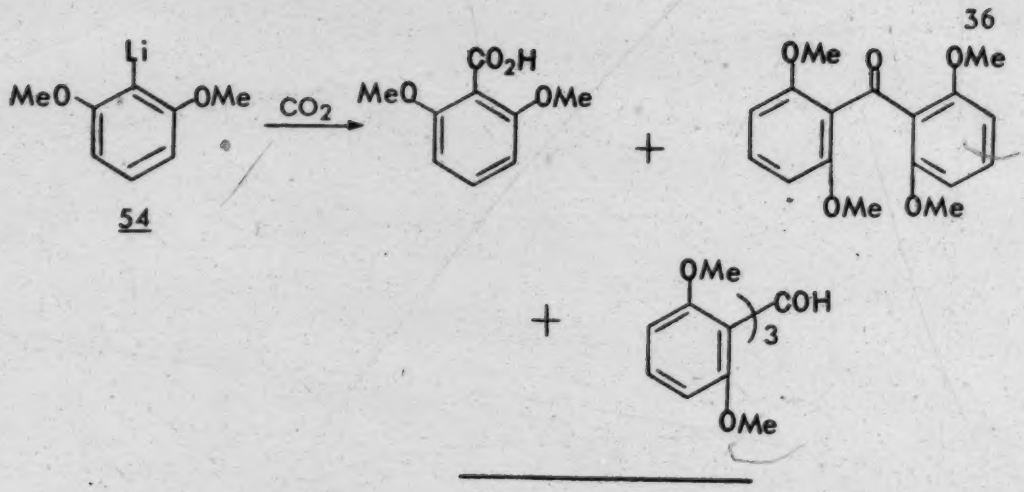


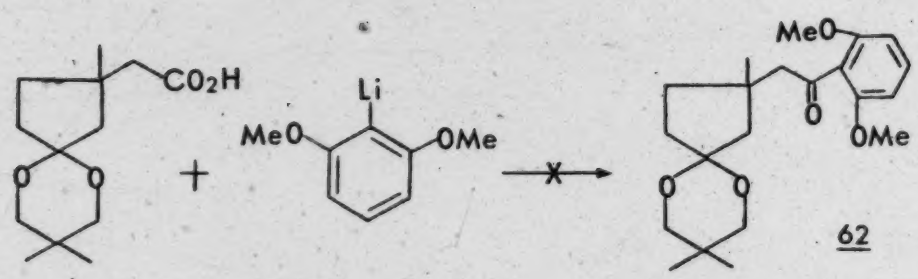
61

over-reaction to produce the alcohol. The stability of the intermediate dilithium compound is invoked as the most plausible explanation.

In light of our inability to produce an amide, the use of this method was investigated. Wittig and Pockels[54] reported that when 54 was treated with CO_2 in an attempt to produce 2,6-dimethoxybenzoic acid, a mixture of products was obtained. The desired acid (14.7%), the ketone derived from the reaction of the acid with 54 (25%) and a trace of triaryl carbinol were isolated.

This we took as an indication that reaction between the acid 61 and 2,6-dimethyloxylithiobenzene might be used to synthesize the ketone 62.

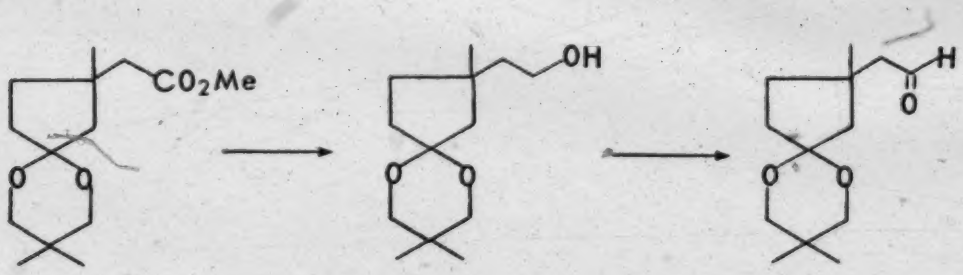




The preliminary investigation of the method did not lead to a successful result. A mixture consisting mainly of starting material was obtained after treatment of 61 with 54. The mixture left after separation of the acid with sodium bicarbonate showed no carbonyl absorption in the ir. This route was abandoned when positive results were obtained by the modified approach described below.

Concurrent with the first failure in obtaining the ketone 62, we started the preparation of 2,8,8-trimethyl-6,10-dioxaspiro[4.5]decane-2-acetaldehyde 64. We expected that the aldehyde would not present the problem of over-reaction

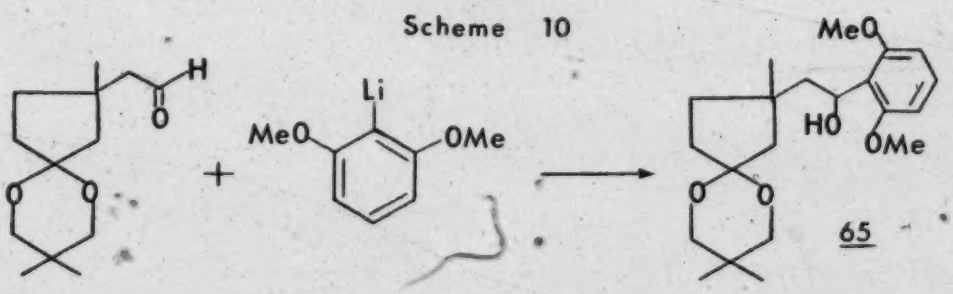
that we encountered when using 59. The aldehyde should be readily accessible by oxidation of the corresponding alcohol 63, itself prepared in high yield by lithium aluminum hydride reduction of the ester 59.



59 63 64

Our intention (shown in Scheme 10) was to react the aldehyde 64 with 54 or the corresponding Grignard reagent to obtain the benzylic alcohol 65. The alcohol should be amenable to hydrogenolysis to produce an aromatic compound which in turn might be converted to the desired 1,3-dione.

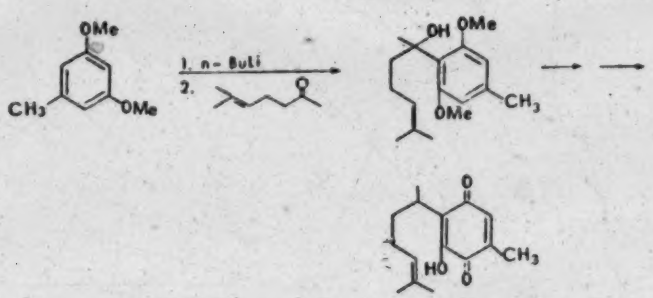
Scheme 10

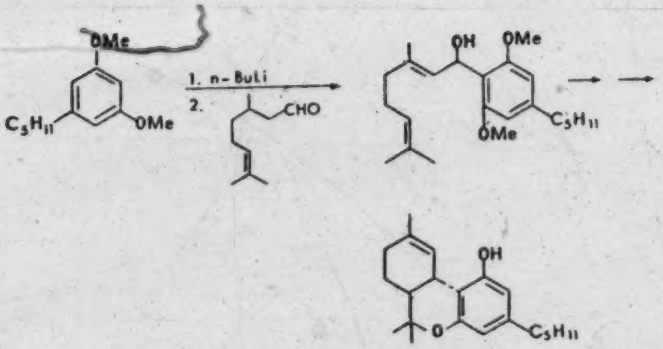


65

There are examples where a similar reaction has been employed. The synthesis of perezone by Cortés, Salmón

and Walls[55] and the synthesis of d,l-Δ^1tetrahydrocannabinol by Mechoulan and Gaoni[56] make use of the reaction between a carbonyl compound and a lithiated 2,6-dimethoxybenzene.



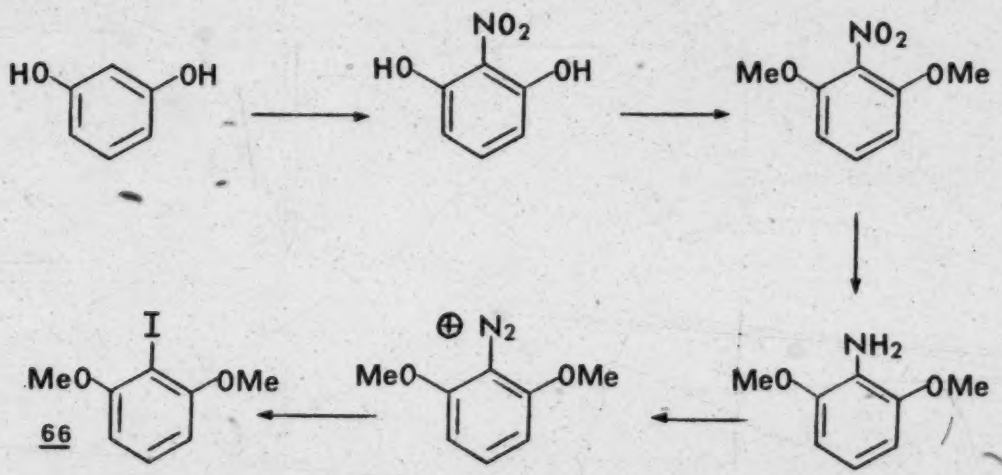


Because of the complex results previously obtained while using 2,6-dimethoxylithiobenzene, we suspected that the aryllithium was only partially formed under our reaction conditions. Thus a mixture of aryl- and alkyllithiums present could, in part, explain the fact that mixtures were consistently obtained whenever we employed the reagent.

In order to avoid this problem, 2,6-dimethoxyiodobenzene 66 was synthesized. The preparation as described in Scheme 11, had previously been reported[57]. A modification to the first step was used as described by Carpenter, Easter

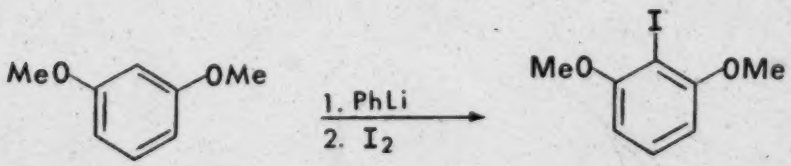
and Wood[58]. The route has one practical shortcoming, the nitration step is rather cumbersome. Also the reported yield of 40 - 45% could not be duplicated. In our hands only a 21% yield was obtained.

Scheme 11



66

A simpler and better preparation of 65 was later employed. The synthesis as described by Boltze, Dell and Jansen[59] involves the metalation of m-dimethoxybenzene followed by addition of iodine. The yield of 66 obtained is high (70%) and the reaction can be carried out successfully on a large scale.



The preparation of the ketal-aldehyde 64 was attempted in several ways. Moffat-Pfitzner oxidation[60] of

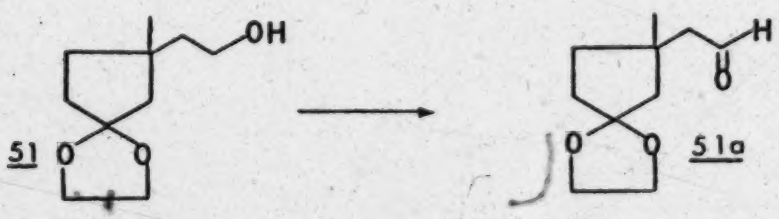
the alcohol 63 using trifluoroacetic acid afforded a 95% yield of crude aldehyde. While the product seemed to be pure (tlc) the nmr spectra showed several broad signals that were not compatible with the expected nmr of the aldehyde. Chromatography on alumina afforded the pure aldehyde in only 40% yield. A small quantity of N-trifluoroacetyldicyclohexylurea was also isolated. The use of anhydrous phosphoric acid (prepared by addition of phosphorous pentoxide to 85% H_3PO_4) was more advantageous than that of trifluoroacetic acid. The crude aldehyde obtained by this modification (85 - 92%) although contaminated (presumably with dicyclohexylurea) was used successfully in the next reaction.

After we had established the efficacy of the Grignard reactions and the subsequent removal of the benzylic hydroxyl group (described later), we decided to prepare the aldehyde by a different method. Our reasons were twofold. First the Moffat-Pfitzner oxidation uses an excess of dicyclohexylcarbodiimide. This reagent has to be destroyed by conversion to the urea and the latter removed. In our hands the aldehyde was always contaminated due to incomplete removal of by-products. Furthermore, the process is cumbersome. Finally we felt that the use of a purer aldehyde would improve the yield in the subsequent Grignard reaction.

Recently Corey and co-workers have reported the use of a DMSO-Cl_2 complex for the oxidation of primary and

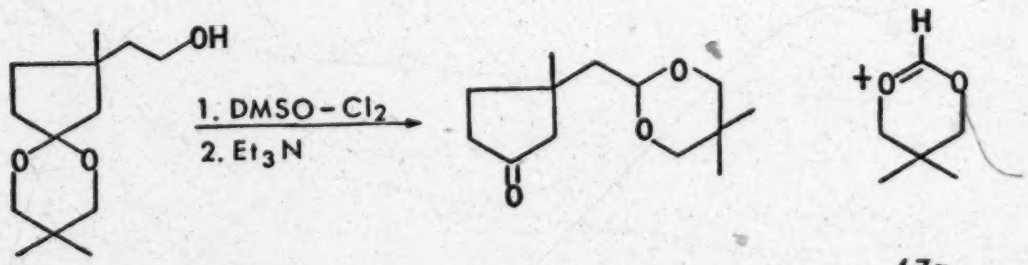
secondary alcohols to the corresponding carbonyl compounds[61]. This method was attractive because: a) it is believed to proceed through an intermediate similar to the intermediate postulated for the DCC-DMSO oxidation (which we already knew to be successful) b) the by-products, DMSO and triethylamine hydrochloride, are easily removed by aqueous washings.

The first compound on which we attempted the oxidation was 51. The reaction proceeded without complications to give 7-methyl-1,4-dioxaspiro[4.4]nonane-7-acetaldehyde 51a in 65% yield and in very pure form.



When the same reaction was carried out using alcohol 63, the results were quite different. Under the same conditions used for 51, 5 mmoles of 63 was oxidized to obtain a mixture of compounds. The mixture showed, instead of the expected ir absorptions at 1725 and 2720 cm^{-1} (aldehyde), a strong absorption at 1745 cm^{-1} (cyclopentanone or ester). Separation by column chromatography (silica gel) afforded 36% of a slightly impure oil. This oil is believed to be 67

on the basis of the following observations. Its ir shows a strong carbonyl absorption at 1750 cm^{-1}. The compound is reduced by sodium borohydride to give a product of higher polarity on tlc. This product does not show carbonyl absorption in the ir but shows strong hydroxyl absorption (broad, 3450 - 3350 cm^{-1}). An exact mass determination of the parent peak of 67 is consistent with a compound with the empirical formula $C_{13}H_{22}O_3$ (Calcd: 226.1564 Found: 226.1569). The base peak at m/e 115 corresponds with 67a. Neither 67 nor the oxidation procedure were further examined.



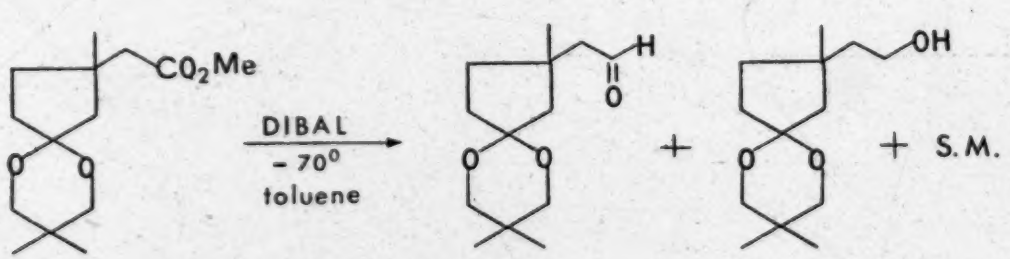
63 67 67a

The use of the N-chlorosuccinimide-dimethylsulfide complex for the same oxidation, another of Corey's methods[62], was briefly examined. This also led to a complex mixture of products.

The direct conversion of the ester 59 to the desired aldehyde 64 was attempted with limited success. Certain complex hydrides may be used to prepare aldehydes.

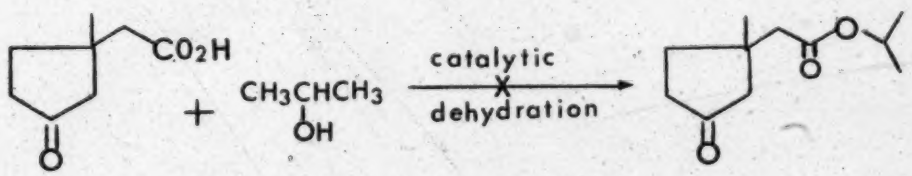
from esters. Reputedly treatment of aliphatic esters with sodium aluminum hydride at temperatures of -45 to -60° using THF as the solvent gives rise to the aldehyde in good yield[63]. It is reported that aromatic esters give lower yields. The use of Red-al, sodium bis(2-methoxyethoxy)aluminum hydride[64] or diisobutylaluminum hydride, DIBAL[65] brings about the same type of conversion.

The use of the last two reagents was explored. Treatment of 59 in ether for five hours at -78° with Red-al led to no reaction and the starting material was recovered unchanged. The same result was obtained after treatment at -40° for the same period of time. Diisobutyl aluminum hydride proved to be more effective than Red-al. Unfortunately, however, clean conversion to the aldehyde could not be achieved. Instead a mixture of aldehyde, alcohol and starting material was isolated. Thus addition of DIBAL to a solution of 59 in toluene at -70° (the temperature was not allowed to warm above -60°) followed by rapid addition of methyl alcohol to quench the reaction led to a 5:2:3 mixture of 64, 63 and 59.



59 64 63

The previous workers[65] state that increased bulkiness of the alcohol portion of the ester minimizes over-reduction. In an attempt to achieve a clean conversion to the aldehyde we attempted to prepare the isopropyl ester. In this case the catalytic dehydrator did not bring about the desired conversion. No further attempts to prepare the ester were made.



The method that was most effective for the oxidation of the alcohol 63 to the aldehyde 64 involved the use of chromium trioxide-pyridine complex. In 1970 Ratcliffe and Rodehorst published an improved procedure for oxidation with $CrO_3 \cdot Py_2$ complex[66]. The preparation of the $CrO_3 \cdot Py_2$ directly in CH_2Cl_2 avoids the need of storing the very hygroscopic complex after preparation. A slight modification of their work-up procedure (which calls for removal of pyridine by acid wash) consistently afforded very pure 2,8,8-trimethyl-6,10-dioxaspiro[4.5]decane-2-acetaldehyde 64 in high yield (82%).

The Grignard reaction between the aldehyde 64 and 2,6-dimethoxyiodobenzene 66, takes place readily. A

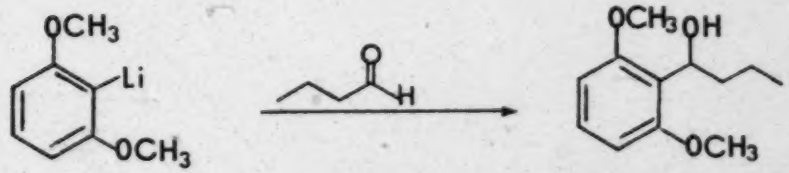
necessary precaution is that of using surface-cleaned magnesium metal and a trace of iodine in order to initiate the formation of the Grignard reagent. Otherwise, the reaction is sluggish and the yield decreases considerably. Dry-column chromatographic separation of the product afforded the alcohol 65 as an oil (55%). The product is a mixture of epimers and could not be crystallized.

Some attempts were made to remove the hydroxyl group by hydrogenolysis. Hydrogenation in ethanol at atmospheric pressure for 18 hours afforded only recovered starting material. Hydrogenation in ethanol at 30 psi over palladized charcoal for four hours was equally unsuccessful. The use of acid is known to promote hydrogenolysis[67]. In our case, extensive decomposition took place when using methanol containing 1% H_2SO_4.

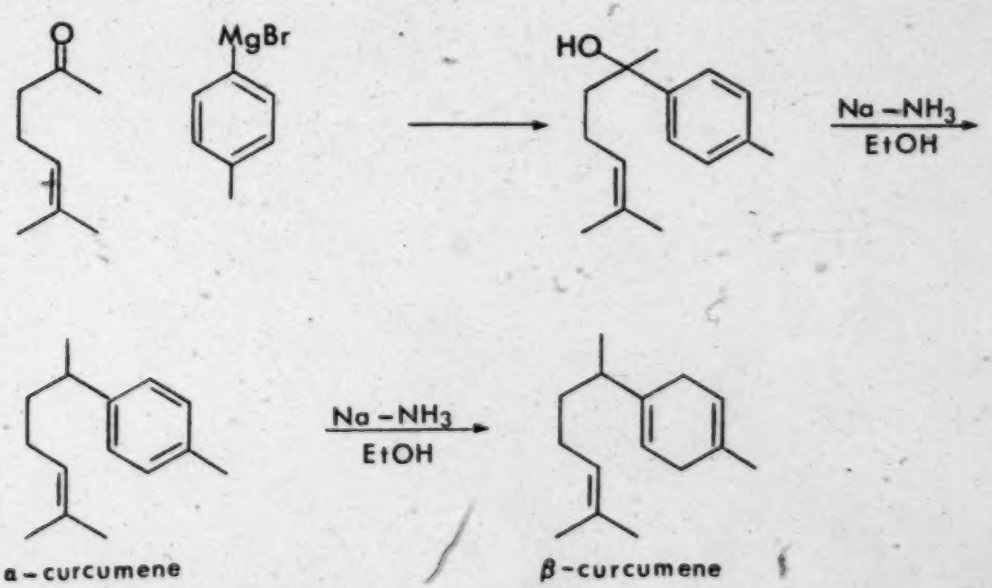
The transformation of the alcohol to a chloride and to a p-toluenesulphonate was then attempted. We expected that the chloride or p-toluenesulphonate should be easily removed by treatment with lithium aluminum hydride. The formation of the p-toluenesulphonate could not be accomplished (p-toluenesulphonyl chloride in dry pyridine) possibly due to steric hindrance. Treatment of 64 with thionyl chloride in pyridine led to a mixture of products which was not further investigated.

At this stage, with the amount of benzylic alcohol

running low, a model compound was prepared in order to define the conditions of hydroxyl removal. Treatment of butyraldehyde with 2,6-dimethoxylithiobenzene gave a low yield (26%) of 1-(2,6-dimethoxyphenyl)-1-butanol.

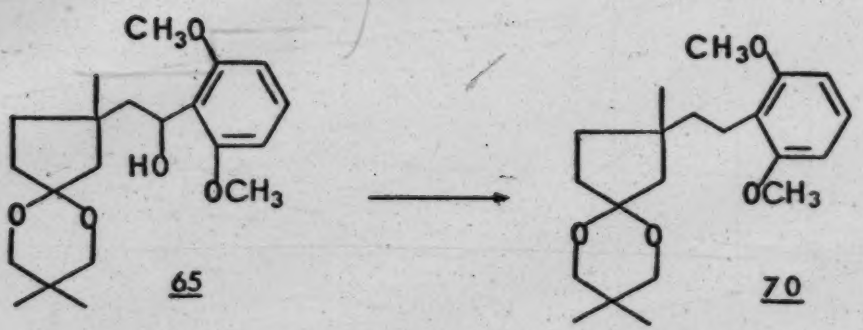


Since catalytic hydrogenolysis was not effective we investigated dissolving metal reduction. Birch reported in 1945[68] that allylic alcohols undergo reductive cleavage by treatment with sodium/ethanol/ammonia. Benzylic alcohols were analogously cleaved under the same conditions. In 1949 Birch and Mukherji made use of these reductions for the synthesis of α- and β-curcumene[69].



Under these conditions 1(2,6-dimethoxyphenyl)-1-butanol was cleaved to obtain 2,6-dimethoxy-n-butylbenzene 68 in high yield (92%). When the alcohol 65 was used as the substrate the corresponding dehydroxylated compound was obtained in good yield. Thus 2-[2-(2,6-dimethoxyphenyl)ethyl]-2,8,8-trimethyl-6,10-dioxaspiro[4.5]-decane 70 was obtained in yields ranging from 82 - 98%.

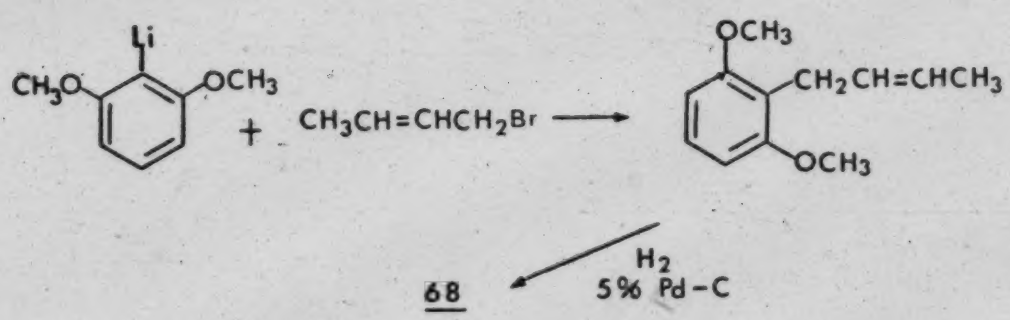
68



65 70

The next step, Birch reduction of the aromatic nucleus, was first investigated using 68 as the model compound. Larger quantities of 2,6-dimethoxy-n-butylbenzene were prepared by a more efficient sequence than previously. Treatment of 1-bromo-2-butene with 2,6-dimethoxylithiobenzene led to the formation of 1-(2,6-dimethoxyphenyl)-2-butene in 40% yield. Catalytic hydrogenation over palladized

charcoal afforded 68 in nearly quantitative yield.



The transformation of 68 to its dihydroaromatic compound 69 was attempted a number of times. Some of the conditions employed and the results obtained are summarized in Table 2. Birch and Russell have reported the reduction of 2,6-dimethoxytoluene[70]. A ratio of 7.85 mmoles of lithium to 1 mmole of aromatic compound was used by those authors. Their product was shown to contain 85% of 2,4-dimethoxy-3-methylcyclohexa-1,4-diene. It is not stated whether the remaining 15% is starting material. Rogers and co-workers have also reduced 2,6-dimethoxytoluene using a different set of conditions[71]. These authors claim 90% conversion to the dihydroaromatic compound.

As can be seen in Table 2 we were not able to obtain a quantitative conversion of 68 to 69. Furthermore, the results obtained were not reproducible. For example, when 1 mmole of 68 in tetrahydrofuran-t-butyl alcohol (10 mls each) was treated for six hours, an 82% yield of a 15:85 mixture was obtained.

TABLE 2

	68 (mmoles)	Co-solvent (ml)	Ammonia (ml)	Metal[a] (mmole)	Proton[b] source (ml)	Time (hours)	Yield %	Ratio 68:69
1	4	--	50	108(Na)	EtOH (1.4)	5	93	90:10
2	4	DME (3.5)	75	154	MeOH (to quench)	3	89	85:15
3	10	THF (5)	50	43	t-BuOH (5)	5	95	60:40
4	5	THF (5)	15	86	t-BuOH (5)	5	84	40:60
5	5	THF (2.5)	15	86	t-BuOH (2.5)	5	74	90:10
6	5	THF (2.5)	15	43	t-BuOH (2.5)	5	80	25:75
7	5	THF (2.5)	15	43	t-BuOH (2.5)	8½	71	20:60
8	5	THF (2.5)	100	215	MeOH (to quench)	6	65	85:15

a. Lithium unless specified otherwise.

b. Unless specified otherwise, the amount of alcohol shown was present at the outset of the reaction. After the time indicated the reaction was quenched by addition of more alcohol

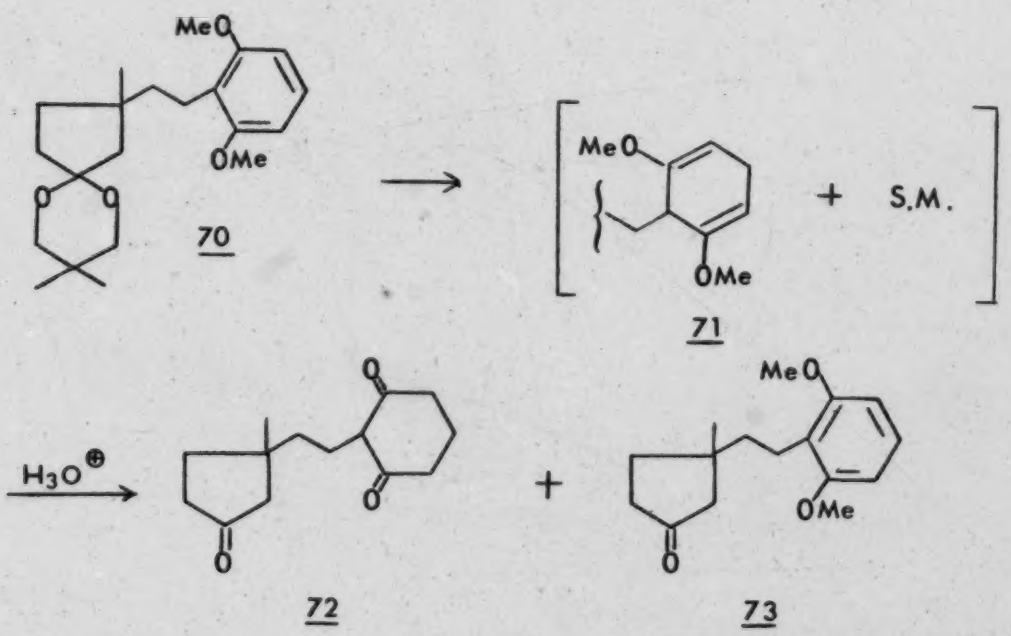
Recently Kwart and Conley reported a modified Birch reduction using lithium in alkylamines[72]. These authors found that the amount of reduction was proportional to the amount of metal used. The concentration of the proton source or the alkylamines seemingly had no effect. The method was used anticipating that the use of an excess of metal would lead to the desired product. While increased amounts of dihydroaromatic compound were actually obtained by increasing the amount of lithium used (see Table 3), complete conversion to the dihydroaromatic compound could not be effected.

TABLE 3

To 68 (4 mmoles) dissolved in n-propylamine (30 ml) lithium and t-butyl alcohol were added at intervals.

	Lithium (mmoles)	t-butyl alcohol (ml)	Time (hours)	Condition	Yield	Ratio 68:69
1.	14.5	15	5	room temp.)	77%	65:45
	14.5	15	4	" ")		
2.	14.5	15	4	reflux)		
	72.5	75	4	")	75%	35:65
	29.0	30	2	")		
3.	29	30	2	reflux)		
	29	30	2	")		
	29	30	1½	")		
	29	30	1½	")	54%	20:80
	29	30	1½	")		
	29	30	1½	")		
	29	30	2	")		

Although the conditions defined on the model system were not ideal the reduction of 70 was nonetheless attempted. We anticipated that on hydrolysis of the product a mixture of two compounds, 72 and 73, would be formed. We reasoned that the separation of 72 from 73 would be facile and that 73 could then be recycled.



When 70 was treated for three hours with Li-NH_3-^{t}BuOH using THF as co-solvent, a 1:1 mixture of 70:71 was obtained. This mixture was treated once more using the same reduction conditions. The 1:3 mixture of 70:71 thus obtained was heated in 10% HCl for three hours. Extraction with ether afforded a complex mixture of products which proved difficult to separate. A simpler method was sought.

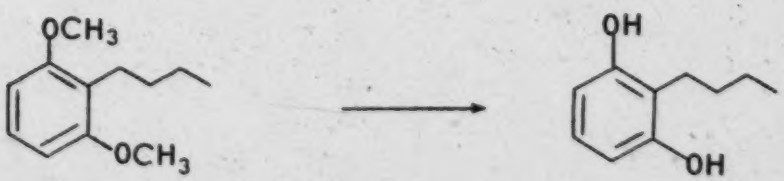
The catalytic hydrogenation of resorcinol in dilute aqueous sodium hydroxide over nickel-nickel oxide-kieselguhr

at 1000 - 1500 pounds produces 1,3-cyclohexanedione in 85 - 95% yield[73]. The necessity for high pressure hydrogenation conditions may be avoided by the use of rhodium on alumina as the catalyst. Using this catalyst comparable yields of the dione are obtained at only 50 psi of hydrogen[74]. If a similar reduction could be accomplished using a 2-alkyl substituted resorcinol, the preparation of 72 could then be achieved after transformation of 70 to the corresponding resorcinol.

In order to test this possibility, commercially available 2-methylresorcinol was hydrogenated using the same conditions reported by Meyers[74]. In this manner 2-methyl-1,3-cyclohexanedione was obtained in 63% yield. The reaction conditions were not optimized but the yield was sufficiently high to warrant consideration of this method as a viable alternative route to 72.

The ether cleavage was investigated using 68 as the model compound. The cleavage of ethers has been extensively studied[75] and there are a number of methods available to effect this transformation. Treatment of 68 with a mixture of 48% - HBr and glacial acetic acid at reflux temperature for eight hours afforded 2-n-butylresorcinol 74 in 42% yield. Treatment of 70 under the same conditions led to extensive decomposition. When a mixture of pyridinium hydrochloride and 68 was heated under reflux (230°) for three

hours[76] an 86% yield of the resorcinol 74 was obtained. Heating a mixture of 68 and methylmagnesium iodide at 180° for seven hours[77] produced 74 in 96% yield. Disappointingly these methods gave complex mixtures when used with 70. Other methyl ether cleavage methods were attempted on 68 without success. These were: a) treatment of the ether at 185° in a Carius tube with 10% aqueous methylamine[78] b) heating to reflux in diethylene glycol in the presence of potassium thiophenoxide-thiophenol[79] 3) treatment with boron trichloride[80]. The first method gave a mixture of compounds, the last two afforded unchanged starting material.

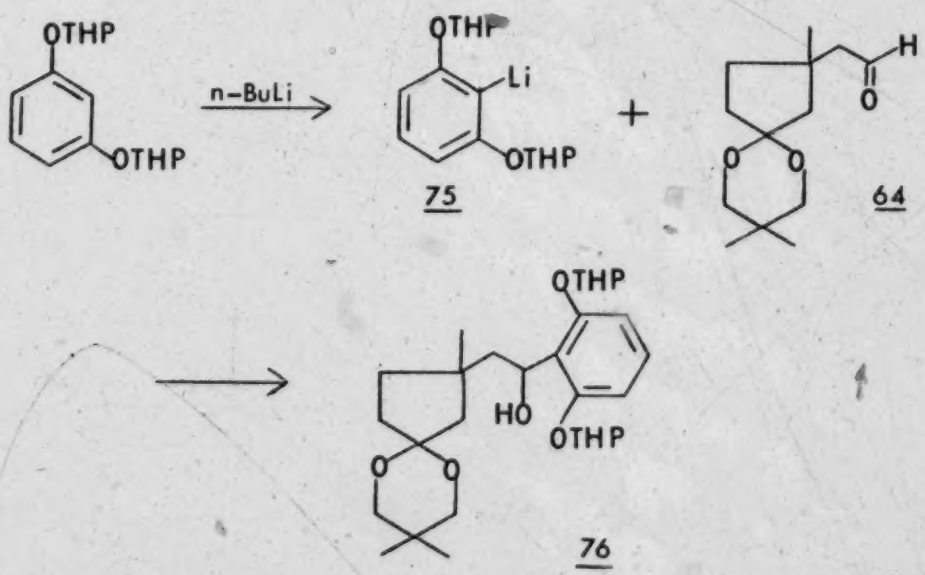


74

One way to circumvent the ether cleavage would be to use a protecting group which could be removed under mild conditions. If instead of using 2,6-dimethoxylithiobenzene one were to use bis(tetrahydropyran-2-yl)-2-lithioresorcinol in the same sequence of reactions employed to prepare 70, the final product should hydrolyze readily to the desired resorcinol.

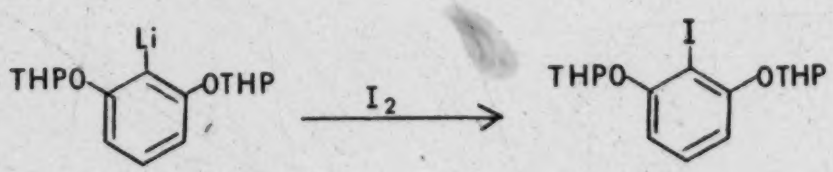
Parham and Anderson have reported the preparation of bis(tetrahydropyran-2-yl)-2-lithioresorcinol 75. These

authors were able to prepare 2,6-dihydroxybenzoic acid in 86% yield by treatment of 75 with CO_2 followed by hydrolysis [81]. When we treated 75 with the aldehyde 64, the corresponding alcohol 2-[2-(2,6-ditetrahydropyran-2'-yloxphenyl)-2-hydroxyethyl]-2,8,8-trimethyl-6,10-dioxaspiro[4.5]decane 76 could be isolated in 26% yield. The low conversion to 76 and the tedious chromatographic separation involved led us to search for modifications which would improve the efficiency of the sequence.



As in the previous case, we felt that the preparation of bis(tetrahydropyran-2-yl)-2-iodoresorcinol 77 might solve the problem. The preparation of 77 was carried out in the same manner as that of 2,6-dimethoxyiodobenzene. The product, obtained as a yellow solid (40%), decomposed rapidly and could not be characterized fully. Furthermore, its instability made

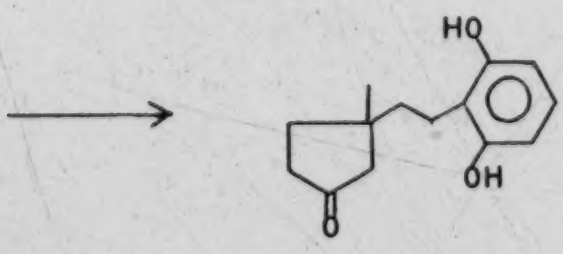
difficult its use in the Grignard reaction. It was found that treatment of bis(tetrahydropyran-2-yl)resorcinol with phenyl lithium afforded 75 as a white solid. Removal of the mother liquor with an hypodermic syringe and rinsing the solid with ether affords 75 sufficiently pure for further reaction with 64. In this manner, 76 was obtained in 79% yield from 64.



75 77

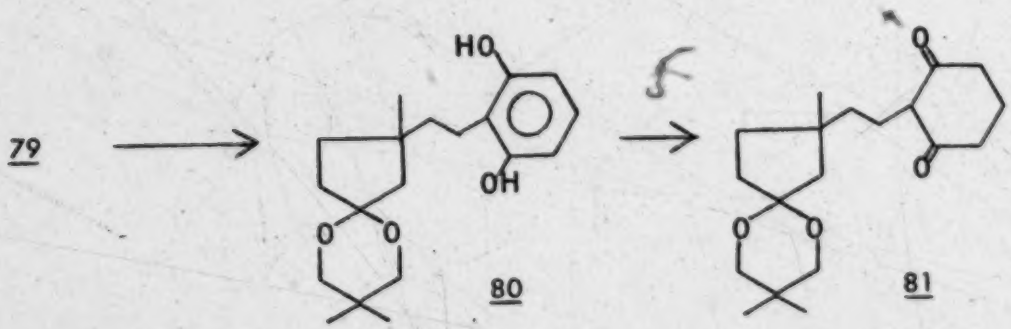
Removal of the benzylic hydroxyl group was achieved in 89% yield using the conditions employed previously. The dehydroxylated compound 78 was easily transformed into the keto-resorcinol 79 in 75% yield by hydrolysis in aqueous methanol containing oxalic acid.

78



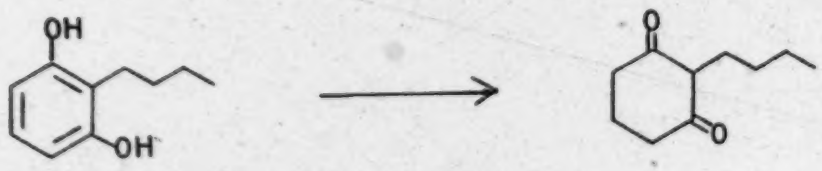
79

Our attempts to selectively remove the tetrahydropyranyl protecting groups without cleaving the ketal met with failure. Surprisingly, the protection of 79 with 2,2-dimethyl-1,3-propanediol was difficult. In a number of cases, a mixture of 80 and starting material was obtained. On standing, the mixture discolors and hydrolyzes to 79. It was found that excess alcohol had to be added at intervals in order to obtain complete conversion to 80. The ketal was obtained as an unstable oil after chromatographic separation on alumina. In order to avoid decomposition it was catalytically reduced to the dione 81 as soon as possible.



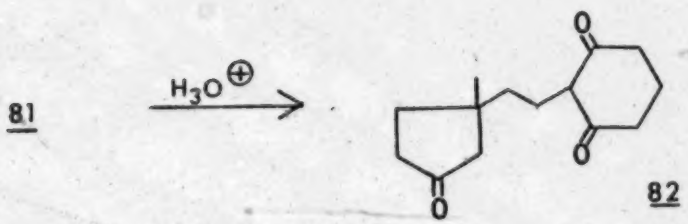
The conditions for the reduction (80 to 81) were first investigated using 2-n-butylresorcinol. This was necessary since the small quantities of 80 available made the use of the Parr hydrogenator impractical. The reduction was carried out using a pressure polymer bottle as the

hydrogenation chamber. The bottle (just wide enough to accommodate asmall stirring bar) was charged with 0.5 mmole of 2-n-butylresorcinol, 10 mg of 5% rhodium on alumina catalyst and 0.55 ml of a 1N NaOH solution. It was then capped and flushed repeatedly with hydrogen before pressurizing to 50 psi. After vigorously stirring the slurry for 18 hours, the reaction mixture was neutralized and extracted with ether to afford a quantitative yield of 2-butyl-1,3-cyclohexanedione.

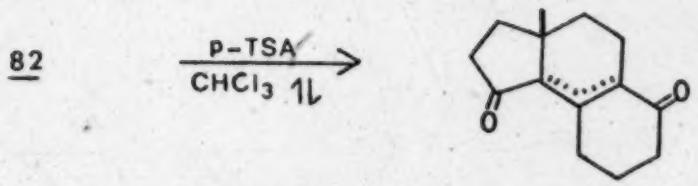


The reduction of 80 was carried out in an analogous manner. Neutralization of the reaction mixture and extraction provided 81 in 96% yield.

At this point we investigated the reduction of the ketone 79 itself to see if the desired cyclization would take place. Hydrogenation of 79 was carried out as on the previous substrate. After acidification a mixture of five components was obtained. The major component appears to be 3-methyl-3-[2-(2,6-dioxocyclohexyl)ethyl]cyclopentanone 82. The ir spectrum of the mixture is very similar to that of 82 obtained by acid hydrolysis of 81.

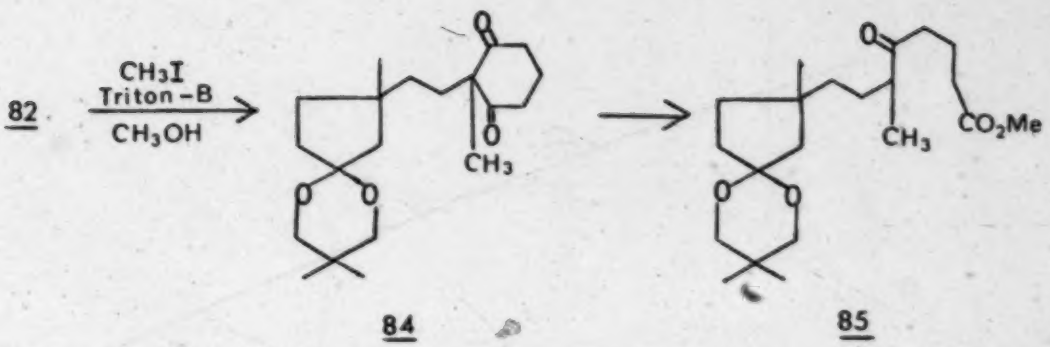


The cyclization of 82 was attempted under a variety of conditions. In most of the cases in which acid-catalyzed cyclization was attempted, mixtures were obtained in which the starting material was the major component. Treatment of 82 under basic conditions led to a poor recovery of a complex mixture. The best results were obtained by heating 82 with p-toluenesulphonic acid in either benzene or chloroform. Thus when 82 (from acid hydrolysis of 20 mg of 81) was refluxed in chloroform containing catalytic amounts of p-TSA, a mixture of products (8 mg) was obtained. Mass spectrometric measurements showed an apparent molecular ion at m/e 218 which would correspond to a tricyclic material such as 83. Preparative thin layer chromatography of the mixture afforded three fractions. One of them (1 mg) gives a molecular ion at m/e 218. The ir spectrum (1730 cm^{-1} shoulder at 1715 cm^{-1} strong, weak bands at 1665 and 1640 cm^{-1}) fits reasonably well with what one would expect from a compound of structure 83.



83

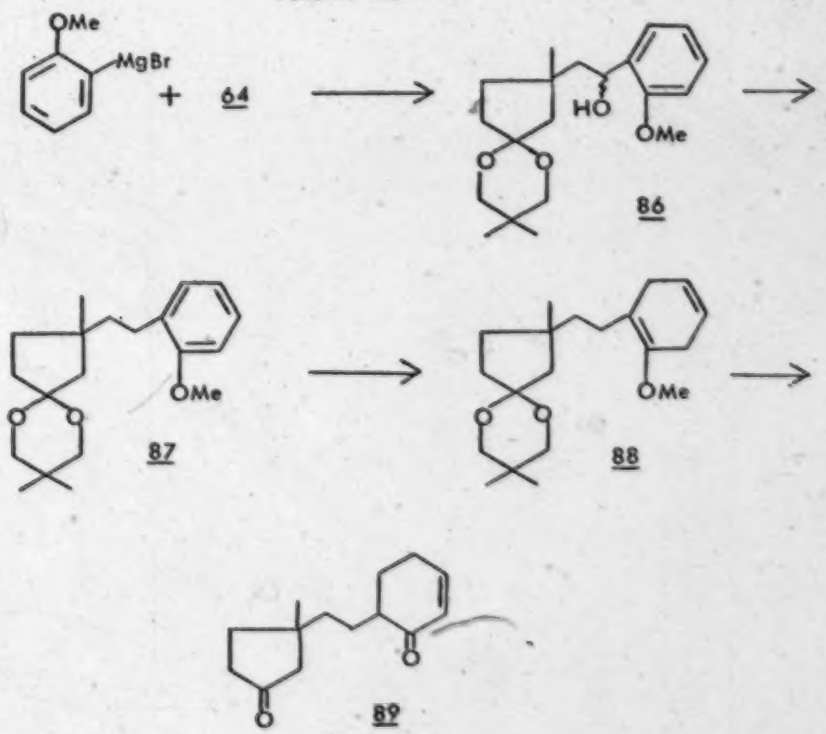
From the results that we obtained it was clear that cyclization does not occur readily, possibly because the tendency of the 1,3-cyclohexanedione to enolize lowers the electrophilicity of the carbonyl group. If this is actually the reason, one way around the problem is to avoid enol formation by methylation at the 2-position of the dione. Alternatively, formation of its enol ether or enol acetate might also facilitate cyclization. Methylation was attempted using methyl iodide in methanol containing Triton-B. The impure product obtained shows carbonyl absorption bands in the ir at 1745 cm^{-1} (ester) and 1710 cm^{-1} (ketone). The mass spectrum shows a prominent peak at m/e 368. These results are consistent with the formation of the keto-ester 85. This material presumably arises by cleavage of the desired methylated diketone 84. In order to isolate 84 without fragmentation the methylation was attempted using potassium t-butoxide-t-butyl alcohol. In this case, however, the mixture obtained showed no indication of the presence of 84, the mass spectrum exhibiting a great number of high-molecular weight peaks.



84 85

In order to further study the cyclization, a simpler system less prone to enolization was synthesized as shown in Scheme 12.

Scheme 12

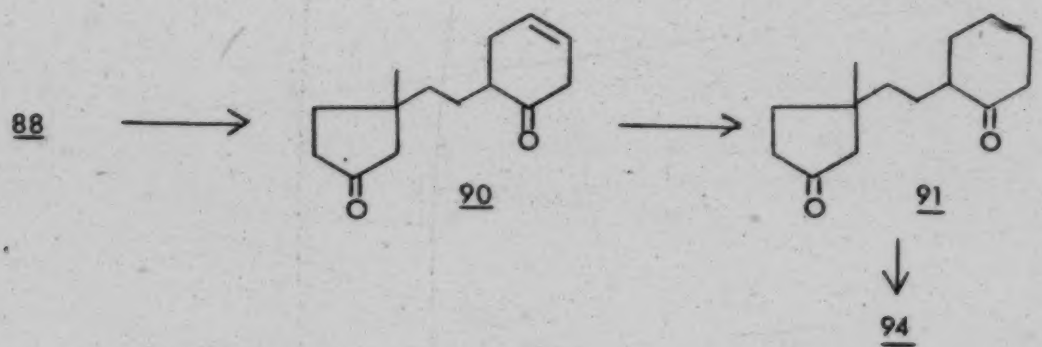


The Grignard reaction between aldehyde 64 and ortho-iodoanisole gives the alcohol 86 in 42% yield together with

2% of the dehydroxylated compound 87. A better yield of the alcohol (53%) was obtained when using THF as the solvent. Reductive cleavage of the benzylic hydroxyl group was achieved in 98% yield using the same conditions employed on previous substrates. The Birch reduction again proved troublesome. When 87 was treated with a 10 molar excess of lithium in ammonia using ether as co-solvent, a mixture of starting material and dihydroaromatic compound 88 was obtained. Acid treatment of this mixture followed by chromatography afforded a 30% yield of impure 3-methyl-3-[2-(1-oxo-2-cyclohexen-6-yl)ethyl]cyclopentanone 89. Our attempts to cyclize 89 under acidic or basic conditions met with failure.

In order to see whether the saturated 3-methyl-3-[2-(1-oxo-cyclohex-6-yl)ethyl]cyclopentanone 91 would undergo cyclization, it was prepared through a modification of the reaction sequence already used. Thus complete reduction of the aromatic ring to 88 was obtained by the use of a 1:50 ratio of substrate to lithium and ethanol. The ir spectrum of the crude 88 lacks the 1600 cm^{-1} absorption due to the aromatic ring. This compound was hydrolyzed under mild acidic conditions to 3-methyl-3-[2-(1-oxo-3-cyclohexen-6-yl) ethyl]cyclopentanone 90. The presence of two carbonyl absorptions in the ir at 1740 cm^{-1} (cyclopentanone) and 1710 cm^{-1} (cyclohexanone) were taken as indication that migration of the double bond to form the α,β-unsaturated

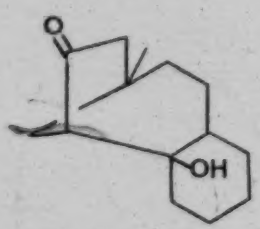
ketone 89 had not taken place. The crude compound was hydrogenated at 30 psi for 30 minutes to the fully saturated diketone 91. (Mass spectrum shows a molecular ion peak at m/e 222.) Without purification this diketone was treated with aqueous methanolic potassium hydroxide to obtain the crystalline tricyclic ketol 94 With the exception of the final product 94 none of the intermediates were purified. In this manner a 50% overall yield of 94 was obtained from 87.



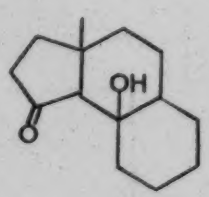
The ketol obtained displays carbonyl absorption at 1740 cm^{-1} (cyclopentanone) and shows a sharp hydroxyl absorption at 3619 cm^{-1} and a weak broad absorption at 3450 cm^{-1}. The signal at 3619 cm^{-1} did not show any change in frequency when the spectra were recorded using 0.05M and 0.01M solutions of 94 in CCl_4. The same appears to be true for the absorption at 3450 cm^{-1} although the signal is quite broad and weak, making a definitive conclusion difficult. These observations

indicate the presence of a free hydroxyl group with possibly some intramolecularly bonded O-H[82]. The nmr ($CDCl_3$) of the ketol shows a sharp methyl absorption at 0.92 ppm. It has been reported[83] that the chemical shift of a methyl group present in a 1,3-diaxial relationship with an hydroxyl group suffers a down-field shift of 0.5 - 1.0 ppm when the spectrum is recorded in pyridine. The methyl absorption of our ketol did not show any shift under these conditions. Apparently in 94 the methyl and hydroxyl groups are not in a 1,3-diaxial relationship.

The diketone may cyclize in such a way as to generate four different skeletal arrangements. Two of them can be discounted as they necessitate the product to have a cyclohexanone. Structures 93 or 94 may represent the isolated product (no stereochemistry shown).



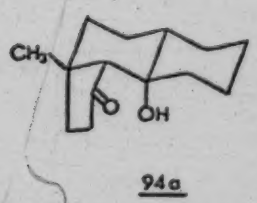
93



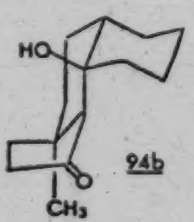
94

We felt that a structure such as 94 would be more likely. It necessitates the formation of a six-membered ring as compared to the seven-membered ring required in the formation of 93. Of the eight possible stereochemical

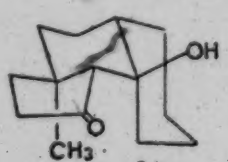
arrangements of 94, three may be excluded as they have a 1,3-diaxial relationship of the methyl and hydroxyl group. Another isomer, trans-syn-trans, can be excluded as it necessitates the central ring in a boat conformation. The four structures left, 94a, 94b, 94c and 94d are arranged in their probable order of stability. Marshall and Fanta[84] have suggested that in aldol cyclizations leading to bicyclic ketols, equatorial attack on the cyclohexanone is preferred to axial attack in the absence of α-substituents. If this is the case, structure 94a represents the actual stereochemistry of our ketol 94. However, at this stage a conclusive assignment cannot be made. Thus the ketol might be represented by structures 94 or 93.



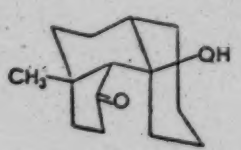
94a



94b



94c

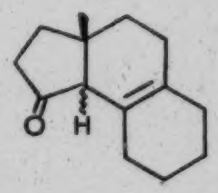


94d

Treatment of 94 in refluxing 10% aqueous potassium hydroxide or with a catalytic amount of p-TSA in refluxing benzene led to a mixture of compounds. The ir spectrum of the mixture showed carbonyl absorption at 1745 cm^{-1}. The nmr showed methyl absorptions at δ 1.04 and 1.23 respectively. No vinyl proton absorption could be detected. The

dehydration product is believed to be the mixture of compounds represented by 95.

94 ⟶

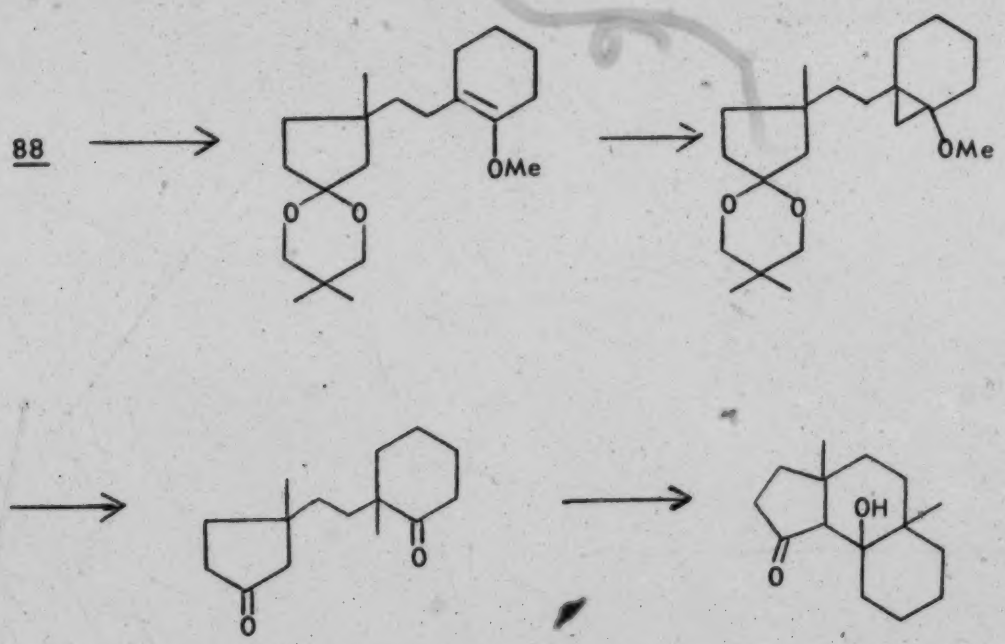


95

Attempts to mono-methylate 95 produced mixtures of mono- and polymethylated compounds as shown by mass spectrometry. We also attempted to form the enol acetate of 95 in an effort to simplify the mixture. However, no clean transformation was achieved on the quantities available.

A method for the preparation of the tricyclic compound having the required two methyl groups was briefly examined. We felt that selective hydrogenation of the less substituted double bond of 88 should be possible. The enol ether obtained could then be cyclopropanylated and this intermediate could in turn be hydrolyzed to yield the diketone 96. Cyclization of this compound might be carried out as on the previous substrate.

Selective hydrogenation proved more difficult than anticipated since 88 shows a great tendency to dehydrogenate to the aromatic compound 87 in the presence of a catalyst.



96 97

This route is being investigated further by another member of the group. If the tricyclic ketol 97 can be obtained efficiently its stereochemistry will be ascertained by X-ray crystallography.

A-B Approach

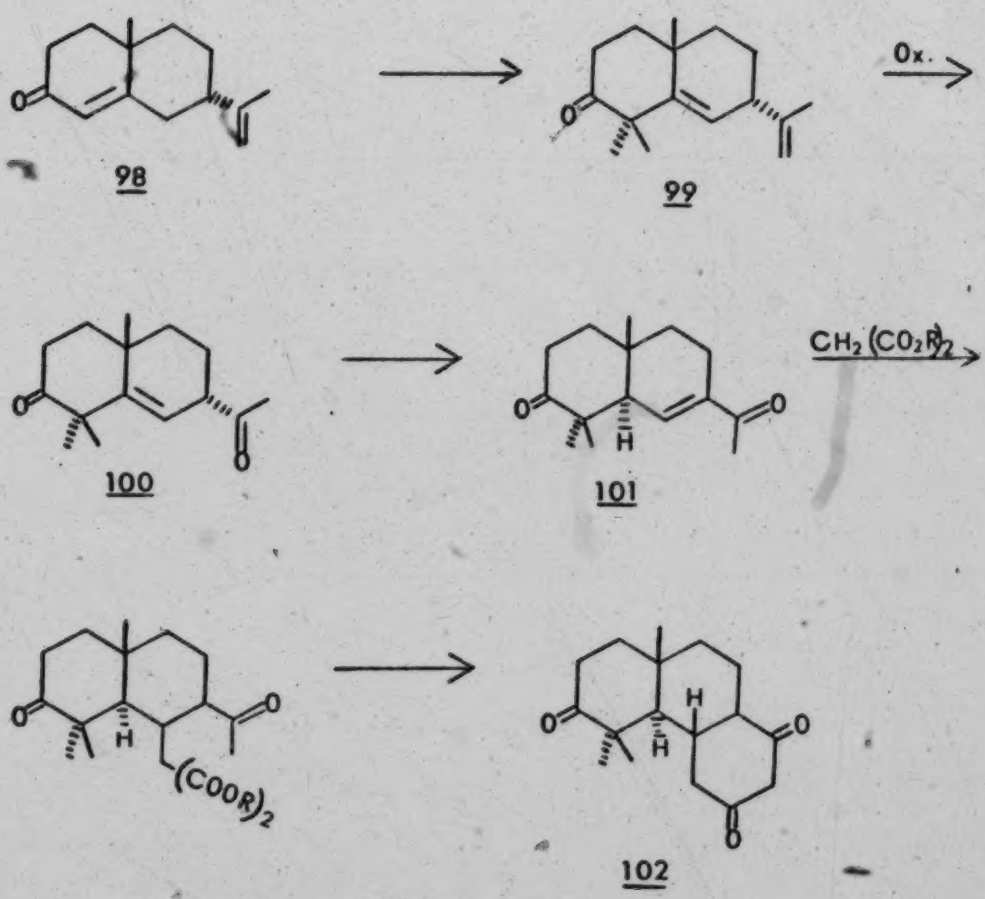
The construction of a two ring system as a suitable starting point for the synthesis of the cyathane skeleton was investigated. Our initial intention was to build two fused six-membered rings that could be modified into rings A and B of cyathin. The precursor to ring A should be functionalized in such a way as to allow a ring contraction to take place leading to a substituted five-membered ring. The

precursor to ring B should be sufficiently functionalized so as to permit the construction of the last ring, ring C. A wealth of information along this line is available from sesquiterpene synthesis[85] as well as from steroid[86] and triterpene synthesis[87].

Specifically 7β(H)-14-noreudesm-4,11-dien-3-one 98 was chosen as our building block. We reasoned that this compound should dimethylated to give 7β(H)-4-methyl-eudesm-5,11-dien-3-one 99. This ketone might be reduced at a later stage to give an alcohol which in turn should contract to the isopropyl substituted ring A of cyathin. The 7α-isopropenyl should be selectively oxidized to form an 7α-acetyl group 100. Subsequent base treatment would lead to the isomeric α,β-unsaturated ketone 101. The ketone might in turn be used as a Michael acceptor when treated with, for example, dialkyl malonate. Final cyclization of this intermediate should generate a tricyclic system 102, a possible synthon to the desired cyathane skeleton. The series of transformations envisioned is summarized in Scheme 13.

In the early stages of this work, the dihydrocarvone required in the synthesis of 98 was obtained by Birch reduction of carvone[88]. Later the reduction was done by the procedure described by Halsall, Theobald and Walshaw[89]. The latter method, using aqueous NaOH, zinc dust and ethanol, has the advantage of being faster. Also greater quantities of carvone could be successfully reduced at one

Scheme 13



98 99 100 101 102

time. A modification of this last method which affords a higher yield of dihydrocarvone was later brought to our attention[90]. Thus dihydrocarvone was obtained in 62% yield by Birch reduction, in 60% yield using Zn/NaOH/EtOH and in 84% yield by Hodgson and Money's modification of the latter method.

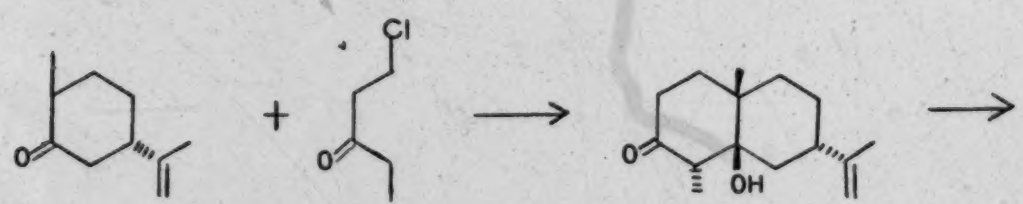
The preparation of 98 was achieved using a modification of the procedure reported by Theobald[91]. Treatment of dihydrocarvone with sosium hydride under nitrogen in refluxing tetrahydrofuran followed by addition of 1-chlorobutan-3-one affords a mixture of starting material, 98, and 5β-hydroxy-7β(H)-14-noreudesm-11-en-3-one 103. Distillation of the mixture separates dihydrocarvone (30 - 50% recovery) from 98 and 103 (58% based on recovered starting material). By treatment of the last mixture for 18 hours under nitrogen in refluxing 10% aqueous potassium hydroxide total conversion to the α,β-unsaturated ketone can be achieved in high yield.

After preparation of the unsaturated ketone, conditions for dimethylation were sought. In 1954 Woodward and co-workers reported the synthesis of lanosterol from cholesterol[92]. The authors reported that direct methylation of either Δ^4- or Δ^5-cholestene-3-one with methyl iodide and potassium tert-butoxide in tert-butyl alcohol readily afforded the 4,4-dimethyl derivative in good yield. Since then a great number of similar reactions have been reported (see reference 3 for some examples in triterpene synthesis). Another base,

potassium tert-amylate[93] in benzene has also been widely used to generate enolate anions from α,β-unsaturated ketones. The methylation was attempted using potassium tert-amylate as the base. The ketone 98 was treated with three equivalents of base and heated at 60° for one hour under nitrogen. After addition of an excess of methyl iodide in benzene the mixture was heated to reflux for one hour. After quenching with acetic acid a mixture was obtained. The mixture showed carbonyl absorptions in the ir at 1712 and 1680 cm^{-1} respectively. The mass spectrum showed molecular ion peaks consistent with the presence of mono-, di- and trimethylated ketone. Somewhat more vigorous conditions were used to convert the mono- to the dimethylated ketone. With increased amount of base (5 eq.) under similar conditions, no monomethylated compound was obtained. A mixture of di-, tri- and tetramethylated ketones with the latter seemingly predominating was obtained instead. Some other variations in the amount of base or methyl iodide were employed but in all of the cases mixtures were obtained.

Expecting to better control the methylation, the synthesis of the monomethylated ketone was carried out. 7β(H)-eudesm-4,11-dien-3-one 105 has been used as the starting point for the synthesis of several sesquiterpenes. The synthesis of α-agarofuran has been carried out by three different groups, all of them using 98 as the starting material[94]. Epi-ν-selinene has also been synthesized

employing 98 as the starting point. A modification of the method described by Halsall, Theobald and Walshaw[89] was used for the preparation of 5β-hydroxy-4β,7β(H)-eudesm-11-en-3-one 104. Thus addition of 1-chloropentan-3-one to a solution of the sodium enolate of dihydrocarvone while maintaining the temperature at -20°, afforded 104 in good yield. The ketol was transformed to 105 by heating to reflux in a 10% aqueous potassium hydroxide solution under nitrogen (95% yield).



104

105 99

Conditions for methylation of 105 were investigated using potassium tert-amylate as the base. When 105 was treated with three equivalents of base followed by the addition of three equivalents of methyl iodide and the mixture heated under reflux for two hours, a mixture was obtained which contained mainly the tetra-methylated ketone.

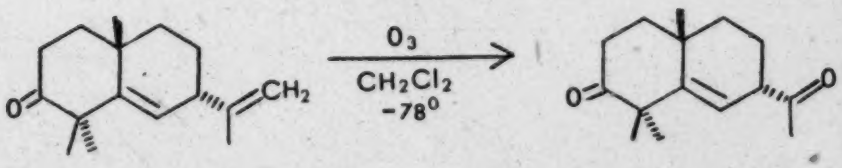
The use of 1.2 equivalents of base and methyl iodide at 0° for one hour led to a mixture of mainly the desired compound contaminated with over-methylated material. No starting material was detected. The di-, tri- and tetra-methylated ketones have similar chromatographic behavior and could not be separated effectively. It was noticed, however, that the R_f's of the starting material and the desired ketone were sufficiently different so that chromatographic separation might be possible. Conditions were sought to produce a mixture of 99 and starting material. The best results were obtained when less than equimolar amounts of base and methyl iodide were used. For instance, a solution of 105 and 0.95 eq. of potassium t-amylate in THF was heated at 60° for 15 to 30 minutes under nitrogen. The solution was cooled to 0° and 0.95 eq. of methyl iodide dissolved in THF was added. The mixture was stirred at 0° for 30 minutes and quenched by addition of acetic acid. A mixture of starting material and the desired compound was obtained in this manner. This mixture was chromatographically separated on silicic acid to yield 80% of 99 together with 15% of starting material. The chromatographic separation was tedious so ways of circumventing this were sought. To this end the use of THF as the co-solvent in the methylation reaction was discontinued. Instead, the use of benzene was investigated. We expected that by decreasing the polarity of the reaction medium the methylation would be appreciably

slower and that over-methylation might be avoided. The reaction required higher temperature (refluxing benzene) and longer periods of time to proceed to the extent of the previous methylation. It was however not advantageous since excess methyl iodide had to be added (to allow for the CH_3I lost through evaporation) and over-methylation could not be avoided. Comparable results to those obtained using THF as co-solvent were secured by treating 105 with equimolar amounts of base followed by addition of a molar excess of methyl iodide and heating the mixture to reflux for one hour.

Methods for selectively oxidizing the exocyclic double bond were now investigated. The internal double bond is more sterically hindered so that oxidation of the non-hindered isopropenyl double bond should take place preferentially. The use of the Lemieux-Von Rudloff reagent ($KMnO_4$-$NaIO_4$) was investigated first[95]. Treatment of 99 with $KMnO_4/NaIO_4/K_2CO_3$ in aqueous t-butyl alcohol led to the isolation of a mixture which no longer showed the presence of vinyl protons in the nmr. Seemingly oxidation of the internal double bond took place under these reaction conditions.

In 1962 Meyer, Cameron and Johnson reported the synthesis of dl-18-norestrone[96]. The synthetic sequence required the use of controlled amounts of ozone. To achieve this, saturated solutions of ozone in methylene chloride were

used. The amount of ozone was controlled by the volume of CH_2Cl_2. This method was used successfully in our oxidation. Thus 1 mmole of 99 was treated with 1.1 mmoles of ozone (40 ml of CH_2Cl_2) to obtain a 43% yield of 4-methyl-7α(H)-noreudesm-4-ene-3,11-dione 100.



99 100

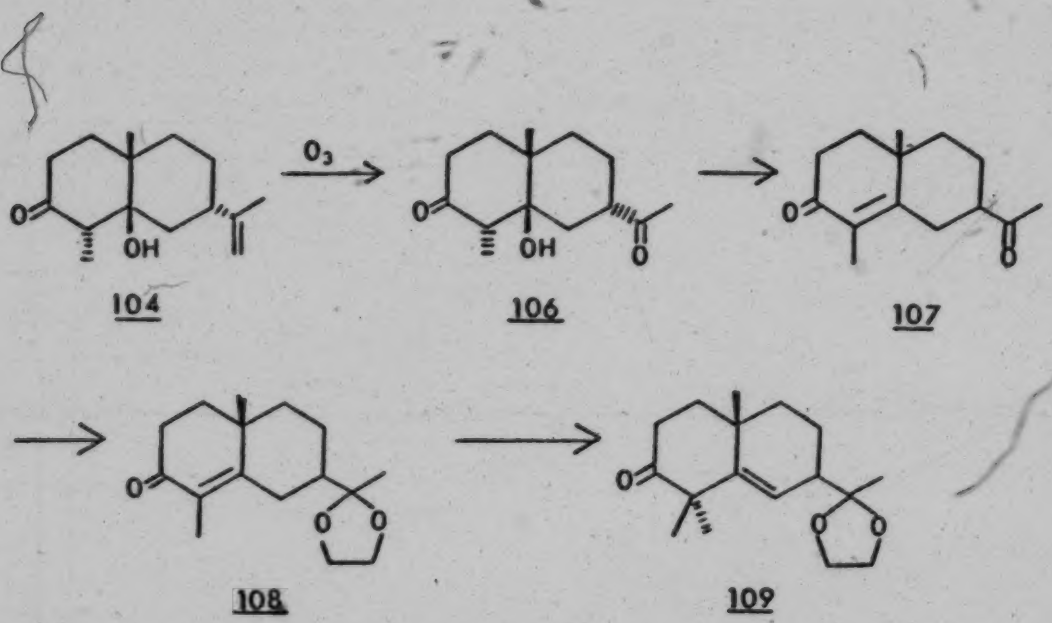
The ozonolysis of large quantities of 99 under these conditions was not practical since large volumes of solvent would be necessary and alternate methods were investigated.

The use of sodium periodate-osmium tetroxide[97] was investigated. Treatment of 99 in ether with an aqueous solution of sodium periodate (3 equivalents) and osmium tetroxide (0.1 equivalents) afforded, after 48 hours of stirring at room temperature, a mixture containing mainly starting material. The oxidation was then attempted under homogeneous conditions. Treatment of 99 for one hour in aqueous dioxane using the same proportions of $NaIO_4/OsO_4$ led to the complete disappearance of starting material. After work-up a 79% yield of crude dione was obtained. It

was identical with the material produced by ozonolysis of 99.

While the conversion of 99 to 100 was accomplished in good yield, we wanted to avoid the use of the toxic and expensive osmium tetroxide. Thus a different approach to the dione was sought. A possible solution would be that of attempting selective ozonolysis of 105. While the double bond that is conjugated to the carbonyl can undergo ozone cleavage, the conjugation decreases its nucleophilicity thus making it less susceptible to attack. In 1958 Stomp and Johnson reported a method whereby selective ozonolysis of an isolated double bond could be achieved in the presence of an α,β-unsaturated ketone[98]. If the ozonolysis is carried out in the presence of pyridine, a complex between ozone and pyridine is formed. This decreases the electrophilic character of ozone allowing for preferential attack on the more nucleophilic double bond. In our hands, however, no clean conversion of 105 to 107 could be achieved by this method.

Since the ketol 104 was available, the possibility of cleaving the only double bond present seemed like a feasible alternative. We expected that the product obtained would dehydrate giving rise to 7β(H)-12-noreudesm-4-ene-3,11-dione 107. The acetyl carbonyl should preferentially ketalize. The non-protected α-β,unsaturated ketone might then be methylated to produce 109.



104 106 107

108 109

The ozonolysis to produce 5β-hydroxy-4,7β(H)-noreudesmane-3,11-dione 106 took place without difficulty. A solution of 104 in methylene chloride was treated with ozone at -78° until the solution became blue. The mixture was warmed and treated with zinc dust and 2% acetic acid to obtain 106 as a solid. Recrystallization from skelly B-ether afforded the pure compound in high yield.

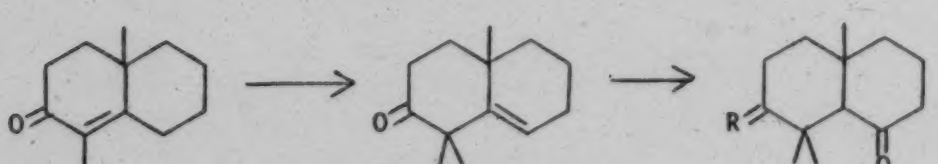
Treatment of 106 in refluxing 10% aqueous potassium hydroxide led to a complex mixture. However, when a solution of 106 in THF containing hydrochloric acid is refluxed under nitrogen, dehydration takes place cleanly. Monitoring the extent of the reaction by tlc, two compounds of lower polarity are formed within minutes. Extended periods of time lead to the exclusive formation of only one compound. We assume that under the reaction conditions the more stable 7β-acetyl

compound is formed.

When the ozonolysis of 104 was carried out on a large scale, a mixture of compounds was obtained which afforded 106 in low yield. Later we found that Hortmann, Martinelli and Wang had already reported the transformation of 104 to 106 and the dehydration of the latter compound to 107. These authors were able to obtain 106 in high yield and on a large scale using a slightly different method[99].

When the difficulties were encountered with the cleavage of the exocyclic double bond, a different approach to an A-B ring system was attempted. We felt that the use of 1,1,4a-trimethyl-1,3,4,4a,5,6,7-heptahydronaphtalene-2-one 111 as the starting material might lead to a more flexible route. Scheme 14 depicts the contemplated sequence.

Scheme 14

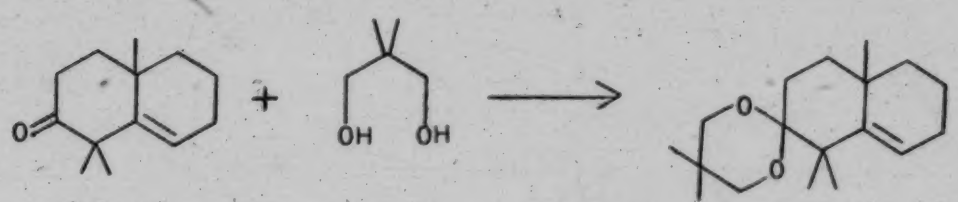


110 111 112

The preparation of 111 has been reported by several groups[100]. Yanagita, Hirakura and Seki report a 25% yield of 111 from 4a-methyl-3,4,4a,5,6,7,8,-heptahydronaphtalen-2-one 113[100a]. For the synthesis of (±)-thujopsene, Dauben and Ashcraft prepared 111 in 77% yield from the same intermediate[100b]. More recently, Paquette and Meehan reported the synthesis of 111[100c]. A mixture was obtained by methylation of 113 from which the pure 111 was obtained via the crystalline semicarbazone. No yield is quoted.

In view of our previous experience, 1,4a-dimethyl-3,4,4a,5,6,7,8-heptahydronaphtalen-2-one 110 was chosen as the starting point. This material was prepared from 2-methylcyclohexanone and 1-chloropentan-3-one using the same conditions as in the synthesis of 98. Mukherjee and Dutta have reported that a clean conversion of 110 to 111[101] can be obtained by treatment with potassium t-amylate and methyl iodide (93% yield). Following their method we obtained a 91% yield of mixture of ketones. The desired 111 was the major compound. The purification method used by Paquette and Meehan[100c] was not employed. Instead, ketalization of the mixture with 2,2-dimethyl-1,3-propanediol was carried out. Using an excess of the alcohol complete ketalization could not be effected. Treatment of the mixture with lithium aluminum hydride and chromatographic separation afforded the ketal of 111 as a crystalline compound, free of

over-methylated material. We had expected that the more sterically hindered ketones present in the mixture would fail to undergo ketal formation. Also we felt that their separation from the desired compound might be facilitated by their conversion to alcohols. While the yield of 114 through this sequence was only 40%, the method provided the protected ketone in the pure form.



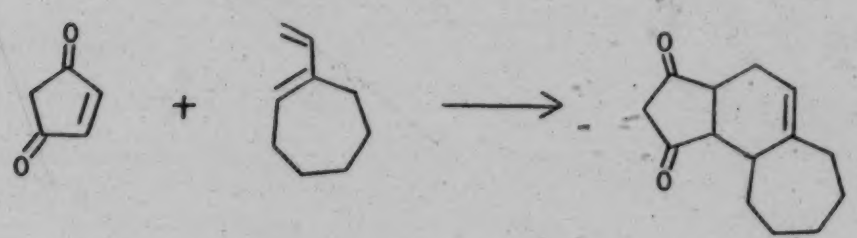
mixture 114

At this point, the investigation of the A-C approach described previously seemed the more promising and the A-B approach has not been carried beyond this point.

Diels-Alder Approach

The Diels-Alder approach to the cyathin skeleton was given only cursory attention. It was found that 4-cyclopentene-1,3-dione condenses with 1-vinylcyclohept-1-ene, prepared by addition of vinyllithium to cycoheptanone followed by dehydration, to give an adduct with properties consistent with structure 115. The nmr (DMSO-d_6) shows a broad absorption at δ 5.38 (vinyl proton) and a complex signal

from δ 2.9 to 0.8. Their integration ratio is 1:17. The ir (KBr) shows a broad band at 3420 cm^{-1} (enol) and a sharp band at 1590 cm^{-1} (carbonyl). A high resolution mass spectrum gives a parent peak consistent with $C_{14}H_{18}O_2$ (calcd. for 218.1307, found 218.1314). The adduct, highly insoluble in most solvents, gives a weakly positive ferric chloride test in pyridine-chloroform.



115

This approach has not been further exploited.

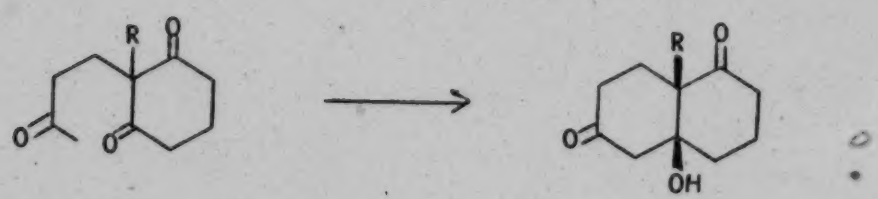
CONCLUSIONS

The results obtained in our study of the A-C approach point out its potential use in the synthesis of the cyathins.

In light of our findings, the ring C precursor to be used in the cyclization step whould probably be limited to those not containing a double bond. This suggestion is based on the finding that substrates 82 and 89 failed to cyclize.

Our initial target, precursor 40 is still an attractive objective. The methyl group present between the carbonyls would avoid extensive enolization, thus facilitating cyclization. Furthermore, it would avoid the problem of selective introduction at a later stage in the synthesis. Another attractive feature of the precursor 40 is that the methyl group would likely direct the mode of cyclization to one of the flanking carbonyls. The steric course of the aldol cyclization has been studied by Spencer, Schmiegel and Williamson[102]. These authors found that 2-acetoxy-2-(3-oxobutyl)-cyclohexane-1,3-dione 116 cyclizes to produce cis-9-acetoxy-10-hydroxydecalin-1,6-dione 117. Later Spencer, Niel, Ward and Williamson[103] reported that 2-methyl-2-(3-oxobutyl)-cyclohexane-1,3-dione 118 gives rise to

cis-9-hydroxy-10-methyldecalin-2,5-dione 119. These authors conclude that steric interference of the substituents in the 2-position directs the approach of the side chain from the opposite side.

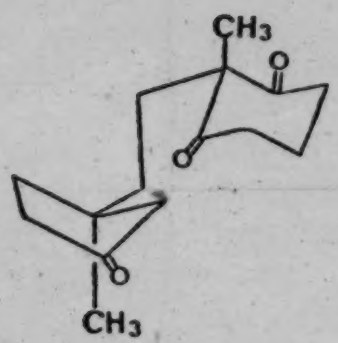


116 R = OAc
118 R = Me

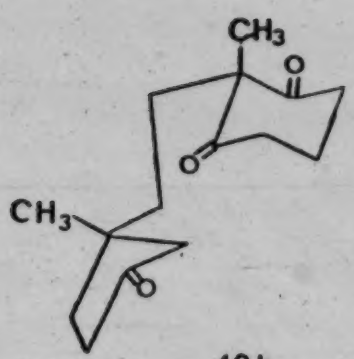
117 R = OAc
119 R = Me

If we make the reasonable assumption that conformations 40a and 40b are preferred conformations for 40, it can be said a priori that conformation 40a, which places the methyl group in the cyclopentanone away from the reaction site, will be the preferred conformation for aldolization. The same argument applies if the side chain is in an axial position. Cyclization of 40a would give rise to a ketol having the methyl groups at the ring junctions in a trans disposition, the desired stereochemistry.

Birch, Smith and Thornton[104] have reported the alkylation of the potassium salt of 1,5-dimethoxycyclohexa-



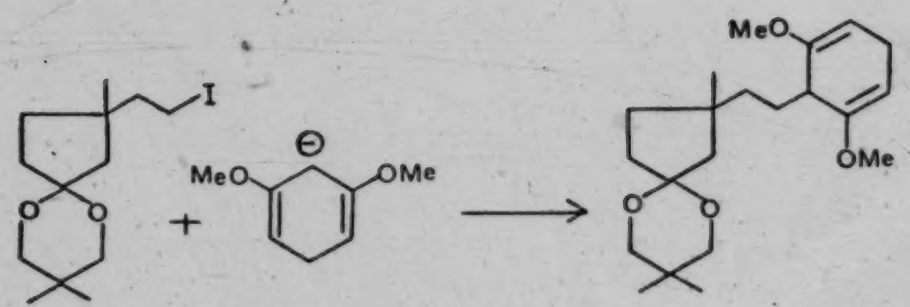
40a



40b

1,4-diene with alkyl halides. This salt has been used by Nelson and Tamura[105] in the synthesis of aza-steroids. It might be useful in the synthesis of the cyathins to obtain larger quantities of 3-methyl-3-[2-(2,6-dioxocyclohexyl)-ethyl]cyclopentanone 82. This material might then be alkylated or cyclized to a suitable intermediate. The use of 1,5-dimethoxy-6-methylcyclohexan-1,4-diene is not possible since Birch and co-workers report that this compound is not sufficiently acidic to form a salt. This problem might be circumvented by the use of an electron-withdrawing substituent such as carboxyl or amide instead of the methyl group. The group could then be modified to a methyl group.

The A-B ring approach still requires further exploration to determine its utility. The fact, however,



that a methyl group will have to be introduced stereoselectively might prove difficult. In this sense the A-C approach may prove to be a more viable alternative to the cyathane skeleton.

EXPERIMENTAL

Melting points were determined on a Fischer-Johns or Leitz-Wetzlar hot-stage melting point apparatus and are uncorrected.

Microanalyses were performed by the Microanalytical Laboratory of this department.

Infrared spectra were recorded on a Perkin-Elmer Model 337 grating infrared spectrophotometer, a Unicam SP1000 grating infrared spectrophotometer, or a Perkin-Elmer Model 421 dual grating infrared spectrophotometer.

Nuclear magnetic resonance spectra were measured using a Varian Associates Model A-60 spectrometer or a Varian Model HR-100 spectrometer with tetramethylsilane as internal standard. Deuterium exchangeable protons are noted in text as D_2O.

Mass spectra were recorded on an A.E.I. Model MS-9 mass spectrometer or an A.E.I. Model GC/MS mass spectrometer with a WB separator.

Chemical ionization spectra were recorded on an A.E.I. Model MS-12 mass spectrometer with a chemical ionization source and ammonia as internal standard.

Preparation of α,α'-dicyano-β-methyl-β-(ethoxycarbonylethyl) glutarimide 45

Absolute ethanol (500 ml) was saturated with ammonia by bubbling the gas for two hours through the magnetically stirred, cooled (ice-water bath) solvent.

To the ammonia-saturated alcohol, an ice-cold mixture of ethyl levulinate[32] (160.5 g, 1.25 moles) and freshly distilled ethyl cyanoacetate (314 g, 2.78 moles) was added in one portion. The passage of ammonia was continued for 20 minutes after the addition. The red, tightly stoppered solution was left in the freezer for four days. The resulting solid mass, was filtered to give 290 g of a pink-coloured solid. This material was dissolved in warm water (400 ml). The solution was acidified by careful addition, with cooling, of concentrated HCl. The oil which separated, soon solidified and was collected (180 g). A second crop of 15 g was obtained after cooling the mother liquor (56.5% combined yield), mp 164 - 165° (lit.[29] mp 169°).

$ir_{(KBr)}$: 1690 - 1730 (C=O), 2250 (CN) cm^{-1}.

$nmr_{(CD_3OD)}$: δ 4.76 (s, 2NCC<u>H</u>, OC-NH, and solvent), 4.16 (q, 2, $COOC\underline{H}_2CH_3$), 1.56 - 1.12 (m, 6, $C\underline{H}_3$ and $COOCH_2C\underline{H}_3$).

mass spectrum: <u>m/e</u> 277(2), 231(21), 176(12), 151(14), 122(15), 94(10), 68(15), 67(13), 45(30), 44(89), 41(100), 40(42), 36(57), 29(46), 28(35).

3-Methyl-3-carboxymethyladipic acid 46

A slurry of α,α'-dicyano-β-methyl-β(ethoxycarbonylethyl)glutarimide (120 g) in concentrated HCl (150 ml), was slowly heated to reflux. The solid dissolved with some gas evolution before reflux began. Refluxing was continued for four days and then hydrochloric acid (approximately 100 ml) was removed by distillation. The resulting brown slurry was dissolved in water (800 ml) and continuously extracted for 48 hours with ether. After the ether was removed, 94 g (99%) of the triacid was obtained, mp 142 - 146° (lit[29] mp 149°). The acid was used in the next step without further purification.

Dimethyl 3-methyl-3-methoxycarbonylmethyladipate 47

The acid resin Rexyn 101(H) R-204 was oven-dried (120°) for 14 hours prior to use. The calcium sulphate (Drierite) was pulverized and oven-dried (200°) for 14 hours before use.

To a solution of 3-methyl-3-carboxymethyladipic acid (22.4 g) in absolute methanol (250 ml), a mixture of calcium sulphate (42 g) and acid resin (18 g) was added. The slurry was mechanically stirred for four days, then vacuum-filtered on celite. The filter cake was stirred in ether (300 ml) for thirty minutes and filtered. After removal of the solvent from the combined methanol and ether

extracts, a dark brown oil remained. The oil was distilled at reduced pressure to give 85% yield of the title compound, bp 131 - 133°/1 mm n_D^{20} 1.4516.

ir$_{(CCl_4)}$: 1740 cm^{-1} (C=O).

nmr$_{(CDCl_3)}$: δ 3.67 (s, 9, $COOC\underline{H}_3$), 2.44((s, 4, $C\underline{H}_2COO$), 2.44 - 2.18 (m, 2, $CH_2C\underline{H}_2COO$), 2.0 - 1.63 (m, 2, $C\underline{H}_2CH_2COO$), 1.1 (s, 3, $C\underline{H}_3$).

mass spectrum: m/e 219(M^+-41,12), 187(21), 155(100), 141(49), 127(54), 123(13), 113(11), 109(10), 95(17), 85(47), 67(14), 59(34), 55(24), 43(17), 41(28), 29(12).

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.23; H, 7.82.

A somewhat better yield (90 - 95%) is obtained if the triester is percolated through alumina (ratio alumina: triester, 3:1). Elution with Skelly B affords 47 in excellent purity.

Methyl 4-methoxycarbonyl-1-methyl-3-oxocyclopentane acetate 48

Xylene (200 ml) was distilled from sodium into an oven-dried one liter 3-neck round bottom flask. The flask was fitted with a magnetic bar, dropping funnel, reflux condenser and a gas inlet-outlet connected to a mercury bubbler. A dry nitrogen atmosphere was maintained throughout the reaction. To the xylene, sodium (2.73 g) was added

and the solvent heated until the metal melted. Vigorous stirring dispersed the sodium into small pellets. To the slurry, dimethyl 3-methyl-3-methoxycarbonylmethyladipate (26 g, 0.1 mole) dissolved in approximately the same volume of xylene, was added in one portion followed by addition of 0.5 ml of absolute methanol dissolved in 10 ml of xylene. A vigorous reaction ensued and heating was discontinued. Once the exothermic reaction subsided (usually 10 - 20 minutes) the yellow solution was refluxed for four hours.

The reaction was cooled and concentrated HCl (15 ml) was slowly added followed by 20 ml of water. After ten minutes of stirring, granulated salt was added until the aqueous layer was saturated. The organic layer was decanted and the aqueous-salt paste rinsed with benzene (3 x 30 ml). The benzene washings were added to the xylene and the solvent removed. A yellow oil (19 g, 84%) was obtained. An analytical sample was obtained after bulb to bulb distillation $180^{\circ}/0.1$ mm n_D^{20} 1.4679.

ir$_{(CCl_4)}$: 2930, 1740 with inflexion at 1750 cm^{-1} (ester and ketone).

nmr: δ 3.75 and 3.70 (2s, 6, $2COOC\underline{H}_3$), 3.43 (t, 1, $O{=}C{-}C\underline{H}{-}C{=}O$), 2.6 - 2.14 (m, 6, $3C\underline{H}_2$), 1.3 and 1.15 (2s, 3, $C\underline{H}_3$).

mass spectrum: m/e 228(7), 197(27), 155(98), 154(53), 141(17), 123(100), 122(80), 114(23), 109(13), 95(32), 87(38), 82(23), 81(14), 67(26), 59(44), 55(77), 53(18), 43(17),

41(46), 39(36), 27(38).

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 58.15; H, 6.89.

1-Methyl-3-oxocyclopentaneacetic acid 49

The crude methyl 4-methoxycarbonyl-1-methyl-3-oxocyclopentaneacetate (19 g) was refluxed in 10% HCl for 14 hours. The solution was cooled and separated from a dark oil floating on the surface. The aqueous phase was then saturated with NaCl and extracted with ether (10 x 50 ml). After the ethereal extracts were washed (brine) and dried ($MgSO_4$) and the solvent was removed, the title compound was obtained as a thick yellow oil (14.2 g, 91%). The acid thus obtained was sufficiently clean to be used without further purification. An analytical sample was prepared by bulb to bulb distillation $170^\circ/0.05$ mm n_D^2 1.4763.

ir$_{(CCl_4)}$: 3100 - 3000 2660 - 2500 (broad, OH of acid), 2960, 1755 (ketone), 1720(COOH), 1415, 1265, 1160.cm^{-1}.

nmr: δ 10.5 (s, 1, COO$\underline{H}$), 2.52 (s, 2, C$\underline{H}_2$COO), 1.8 - 2.4 (m, 6, ring protons), 1.26 (s, 3, C$\underline{H}_3$).

mass spectrum: m/e 156(7), 99(12), 97(100), 96(30), 72(15), 69(24), 67(14), 57(12), 56(20), 55(43), 54(11), 53(21), 45(14), 43(27), 42(21), 41(94), 39(71), 29(33), 28(73), 27(66).

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found:

C, 61.42; H, 7.76.

Methyl 1-methyl-3-oxocyclopentaneacetate 49a

A solution of 1-methyl-3-oxocyclopentaneacetic acid (32 g) in methanol (370 ml), was stirred together with Rexyn 101(H) R-204 (23 g, oven-dried 120°, 12 hours) and calcium sulphate (52 g, oven-dried 200°, 12 hours). After three days of stirring the slurry was filtered and the solid was washed repeatedly with methanol until no more colour could be observed in the washings. The solvent was removed under vacuum to leave 35.6 g of a brown oil. Percolation through a silica gel G column (200 g) using ether as eluent gave a clear liquid (30.4 g, 87%) corresponding to the title compound.

$ir_{(liquid\ film)}$: 1745 cm^{-1} (ester and ketone).

nrm: δ 3.69 (s, 3, $COOC\underline{H}_3$), 2.46 (s, 2, $C\underline{H}_2COO$), 1.8 - 2.4 (m, 6, ring $C\underline{H}_2$), 1.18 (s, 3, $C\underline{H}_3$).

Semicarbazone mp 168 - 170°.

mass spectrum: m/e 227(7), 168(18), 154(100), 137(29), 111(39), 110(59), 109(19), 108(12), 95(16), 94(37), 93(26), 81(24), 80(18), 79(30), 77(16), 69(12), 65(14), 59(23), 54(14), 44(90), 41(80).

Anal. calcd. for $C_{10}H_{17}N_3O_3$: C, 52.85; H, 7.54; N, 18.49.
Found: C, 52.77; H, 7.70; N, 18.65.

Methyl 1-methyl-3-oxocyclopentaneacetate ethylene acetal 50

To a solution of methyl 1-methyl-3-oxocyclopentaneacetate (21.9 g, 0.126 moles) in benzene (600 ml), ethylene glycol (9.3 g, 0.15 moles) and p-toluenesulphonic acid were added. The mixture was refluxed and water azeotropically removed (Dean-Stark trap) for 12 hours. The cooled solution was diluted with benzene (400 ml) and washed with water (50 ml) and brine (50 ml). The dried ($MgSO_4$) solvent was evaporated to obtain the title compound (26.5 g, 98%) as a colourless oil. The compound was used in the following reaction without purification. An analytical sample was obtained by bulb to bulb distillation 160°/0.1 mm n_D^{20} 1.4628.
$ir_{(liquid\ film)}$: 1745 cm^{-1} (ester), 940 cm^{-1} (1,3-dioxolane).
nmr: δ 3.84 (s, 4, OCH_2CH_2O), 3.62 (s, 3, $COOCH_3$), 2.36 (s, 2, CH_2COOCH_3), 2.1 - 1.4 (m, 6, ring CH_2), 1.12 (s, 3, CH_3).
mass spectrum: m/e 214(2), 185(20), 141(41), 113(45), 100(21), 99(100), 97(32), 86(21), 69(23), 59(17), 55(45), 53(20), 43(29), 42(30), 41(53), 39(33).
Anal. calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.90, 61.98; H, 8.72, 8.49.

7-Methyl-1,4-dioxaspiro[4.4]nonane-7-ethanol 51

The ester reduction was carried out under a nitrogen atmosphere. To a solution of methyl 1-methyl-3-oxocyclopentaneacetate ethylene acetal (24.9 g) in dry ether (200 ml),

a 1M solution of lithium aluminum hydride (180 ml) was added dropwise (30 minutes) with cooling (ice-water bath). After the addition was complete, the mixture was left for three hours at room temperature. The reaction was worked-up by the successive dropwise addition of water (8 ml), 15% NaOH (8 ml) and water (15 ml). The white granular solid which separated was filtered and rinsed with ether. The dried (brine, $MgSO_4$) ethereal solution gave the title compound 19.44 g (90%) as a clear liquid n_D^{20} 1.4759.

$ir_{(liquid\ film)}$: 3400 cm^{-1} (alcohol), 940 cm^{-1} (dioxolane).

nmr: δ 3.87 (s, 4, $C\underline{H}_2C\underline{H}_2O$), 3.7 (t, 2 J=7Hz, $C\underline{H}_2OH$), 2.42 (broad s, 1, O$\underline{H}$), 2.2 - 1.34 (m, 8, methylenes), 1.05 (s, 3, $C\underline{H}_3$).

mass spectrum: m/e 186.1257 calcd for $C_{10}H_{18}O_3$, 186.1256. meas(5), 157(77), 141(74), 127(17), 113(54), 100(41), 99(100), 97(14), 86(16), 69(13), 55(30), 43(24), 41(32), 28(33).

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.05; H, 9.75.

7-Methyl-7(2-tosyloxyethyl)-1,4-dioxaspiro[4.4]nonane 52

To a solution of 7-methyl-1,4-dioxaspiro[4.4]nonane-7-ethanol (1.86 g, 10 mmoles) in 15 ml of dry pyridine (distilled from BaO), p-toluenesulphonyl chloride (2.28 g, 12 mmoles) was added with shaking to dissolve the solid. The solution was left in the fridge for 16 hours. After filtering the resulting solid the filtrate was added to water (60 ml)

and stirred (15 minutes). The aqueous solution was extracted with ether (4 x 20 ml) and the ethereal extracts were washed with water (20 ml) and brine (20 ml). A thick oil was obtained after drying ($MgSO_4$) and removing the ether (at room temperature under vacuum). A solution of the oil in Skelly B (200 ml) was treated with charcoal. It was then filtered and slowly cooled to -78° (dry ice-acetone bath). The oil that separated was rinsed twice with Skelly B at -78° to yield a colourless oil (3.0 g, 88%) n_D^{20} 1.5212.

ir (liquid film): 1600 cm^{-1} (aromatic ring), 1360, 1186 and 1175 cm^{-1} (tosyl), 657 cm^{-1} (aromatic ring).

nmr: δ 7.68 (d, 2, aromatic ring), 7.35 (d, 2, aromatic ring), 4.14 (t, 2, $C\underline{H}_2OTos$), 3.86 (s, 4, $OC\underline{H}_2C\underline{H}_2O$), 2.48 (s, 3, aromatic $C\underline{H}_3$), 2.1 - 1.3 (m, 8, rest of $C\underline{H}_2$) 1.0 (s, 3H, CH_3).

Chemical ionization: 358 ($M^+ + NH_4^+$).

7-Methyl-7-(2-iodoethyl)-1,4-dioxaspiro[4.4]nonane 53

A solution of the tosylate 52 (5.1 g, 15 mmoles) in 60 ml of dry acetone ($KMnO_4$-K_2CO_3 distilled), was heated to reflux with sodium iodide (4.5 g, 30 mmoles) for three and a half hours. The solid was filtered and the filtrate evaporated in vacuo. The semi-solid left was partitioned between ether (50 ml) and water (20 ml). The layers were separated and the ethereal layer was washed with 10% sodium thiosulphate (15 ml), water (15 ml) and brine (15 ml).

Removal of the dried ($MgSO_4$) ether gave the crude iodide (4.178 g, 94%). The liquid could not be purified by distillation owing to extensive decomposition. Treatment with charcoal afforded a colourless liquid n_D^{20} 1.5295.

ir (liquid film): 2975, 2880, 1340, 1105 1030, 1015, 935 cm^{-1} (1,3-dioxolane).

nmr: δ 3.85 (s, 4, OCH_2CH_2O), 3.3 - 2.97 (m, 2, CH_2I), 2.18 - 1.32 (m, 8, rest of methylenes), 1.0 (s, 3, CH_3).

mass spectrum: m/e (M^+-109), 187(23), 155(100), 141(50), 127(59), 123(22), 113(22), 109(20), 95(30), 85(59), 67(24), 59(42), 55(35).

Chemical ionization: ($M^+ + NH_4^+$), 314.

Methyl 2,8,8-trimethyl-6,10-dioxaspiro[4.5]decane-2-acetate

59

A solution of methyl 1-methyl-3-oxocyclopentane-acetate (17 g, 0.1 moles), 2,2-dimethyl-1,3-propanediol (11.44 g, 0.11 moles) and p-toluenesulphonic acid (200 mg) in benzene (300 ml), was heated under reflux with azeotropic removal of water for 12 hours. The solvent was removed under vacuum and the yellow liquid was rapidly percolated through an alumina column (100 g, BDH) using Skelly B as eluent. The first 10 fractions (60 ml each) were combined to leave a colourless liquid (22 g, 87%) after removal of the solvent. An analytical sample was secured by bulb to bulb distillation, 180°/0.1 mm n_D^{20} 1.4604.

ir$_{(liquid\ film)}$: 1745 cm^{-1} (ester).

nmr: δ 3.65 (s, 3, $COOC\underline{H}_3$), 3.45 (s, 4, $OC\underline{H}_2C\underline{H}_2O$), 2.34 (s, 2, $C\underline{H}_2COOCH_3$), 2.38 - 1.40 (m, 8, rest of methylenes), 1.12, 0.97 and 0.92 (3s, 9, $3C\underline{H}_3$).

mass spectrum: m/e 256(2), 227(11), 182(22), 155(22), 142(11), 141(98), 139(12), 97(41), 69(100), 56(18), 55(44), 43(16), 41(77).

Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.33, 65.78; H, 9.33, 9.36.

2-(2,2-diphenyl-2-hydroxyethyl)-2,8,8-trimethyl-6,10-dioxaspiro[4.5]decane 60

To a magnetically stirred solution of the acetal 59 (512 mg, 2 mmoles) dissolved in dry ether (8 ml), a phenyllithium benzene-ether solution (2.3M, 1.9 ml) was added dropwise with cooling (ice-water bath). After addition was complete (15 minutes), the mixture was stirred for three hours at room temperature. Saturated aqueous ammonium chloride solution (20 ml) was added and the layers separated. The aqueous layer was extracted with ether (3 x 10 ml) and the ethereal extracts were combined and washed with saturated $NaHCO_3$ (15 ml) and water (15 ml). The solvent was evaporated after drying ($MgSO_4$) to yield 680 mg (89%) of a colourless thick oil that solidified on scratching. Recrystallization from Skelly B gave a white solid mp 95 - 96°.

ir$_{(CCl_4)}$: 3430 (OH), 685 cm^{-1} (phenyl).

nmr: δ 7.63 - 7.12 (m, 10, $2C_6H_5$), 4.44 (s, 4, $OC\underline{H}_2C\underline{H}_2O$), 3.1 (broad s, 1, O$\underline{H}$), 2.56 (s, 2, $C\underline{H}_2CHPh_2$), 2.35 - 1.10 (m, 6, ring methylenes), 0.98 (s, 3, $C\underline{H}_3$), 0.93 (s, 6, $2C\underline{H}_3$).

mass spectrum: m/e 380(2), 198(44), 184(73), 109(22), 141(100), 128(34), 112(31), 105(91), 97(37), 77(57), 69(91), 56(26), 55(67), 41(79).

Anal. Calcd. for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 78.66; H, 8.39.

2,8,8-Trimethyl-6,10-dioxaspiro[4.5]decane-2-acetic acid 61.

A mixture of 1-methyl-3-oxocyclopentaneacetic acid (30.7 g, 0.20 moles), 2,2-dimethyl-1,3-propanediol (21.8 g, 0.21 moles) and p-toluenesulphonic acid (100 mg) in benzene (300 ml), was refluxed with azeotropic removal of water for 14 hours. After removal of the solvent, the residue was dissolved in ether (200 ml) and the ethereal solution was extracted with saturated $NaHCO_3$ (3 x 100 ml). The cold basic extract was acidified with AcOH. The clear oil that separated after acidification was removed, and the aqueous layer was extracted with ether (2 x 50 ml). The oil and ethereal extracts were combined and washed with water (20 ml) and brine (20 ml). On removal of the dried ($MgSO_4$) solvent, a thick clear oil was obtained (219 g, 45%); the oil solidifies on standing in the fridge. The acid is very soluble in most organic solvents. It can be recrystallized from Skelly B

with low recovery. An analytical sample was obtained by substillation 180°/0.05 mm mp 50 - 51°.

ir$_{(CCl_4)}$: 1710 cm^{-1} (COOH).

nmr: δ 10.25 (s, 1, COOH), 3.5 (s, 4, OCH_2CCH_2O), 2.4 (s, 2, CH_2COO), 2.3 - 1.5 (m, 6, ring methylenes), 1.19, 1.0 and 0.94 (3s, 9, $3CH_3$).

mass spectrum: m/e 242(1), 183(21), 155(17), 141(86), 139(12), 83(12), 81(87), 71(11), 69(100), 56(32), 55(57), 53(12), 38(14).

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.56, 64.40; H, 9.18, 9.09.

2,8,8-Trimethyl-6,10-dioxaspiro[4.5]decane-2-ethanol 63

A 1M solution of $LiAlH_4$ (90 ml) was added dropwise with stirring and cooling (ice-water bath) to methyl 2,8,8-trimethyl-6,10-dioxaspiro[4.5]decane-2-acetate (12.8 g). A nitrogen atmosphere was maintained during the reaction. The mixture was stirred at room temperature for three hours after addition was complete (20 ml). After quenching the reaction by consecutive addition of water (4 ml), 15% NaOH (4 ml) and water (6 ml), the granular solid produced was removed and rinsed with ether. The ethereal solution was washed (brine) and dried ($MgSO_4$). The title alcohol was obtained, after evaporation of the ether as a clear oil (10.6 g, 93%). It was used as such for subsequent transformations. An analytical sample was prepared by bulb to bulb

distillation 170°/0.1 mm n_D^{20} 1.4752.

ir (liquid film): 3400 cm^{-1} (OH).

nmr: δ 3.73 (t, 2, J=7.5 Hz, CH_2OH), 3.52 (s, 4, OCH_2CH_2O), 2.6 (broad s, 1, OH), 1.33 - 2.23 (m, 8, rest of CH_2), 1.07 (s, 3, CH_3), 0.98 (s, 6, $2CH_3$).

mass spectrum: m/e 228(1), 183(17), 155(13), 142(12), 141(100), 97(24), 56(18), 55(42), 43(17), 41(63).

Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.19; H, 10.69.

DCC-DMSO oxidation of 2,8,8-trimethyl-6,10-dioxaspiro[4.5] decane-2-ethanol 63

To the title alcohol (250 mg) dissolved in dry DMSO (1 ml), a solution of dicyclohexylcarbodiimide (500 mg) in benzene (2 ml) was added, followed by the addition of 2.5M anhydrous phosphoric acid in DMSO (0.05 ml). After 18 hours of stirring at room temperature, the solution was poured into Skelly B (30 ml) containing oxalic acid (252 mg) and methanol (3 ml), and stirred briskly (30 minutes). It was then neutralized by adding saturated $NaHCO_3$ (10 ml). The resulting dicyclohexylurea was filtered and the layers of the filtrate were separated. After the organic layer was washed with $NaHCO_3$ (5 ml), water (3 x 5 ml) and brine (5 ml), it was dried ($MgSO_4$) and the solvent was removed under vacuum. The yellow oil obtained (240 mg) was percolated through alumina (5 g BDH). The aldehyde (226 mg, 92%) obtained by

this method was always somewhat impure and could not be purified satisfactorily.

ir (liquid film): 2720 and 1725 cm^{-1} (aldehyde).

2-Nitroresorcinol

Resorcinol was converted into 2-nitroresorcinol in 22% yield by the method of Carpenter, Easter, and Wood[58] mp 83 - 84°. (lit. mp 84°).

2-Nitroresorcinol dimethyl ether

2-Nitroresorcinol was converted to the title compound in 76% yield as described by Kaufmann and Franck[57] mp 130°. (lit. mp 130°).

2,6-Dimethoxyaniline

The aniline was obtained in 83% yield by reduction of 2-nitroresorcinol dimethyl ether with Sn-HCl as described by Kaufmann and Franck[57] mp 72 - 73°. (lit. mp 74°).

2,6-Dimethoxyiodobenzene

The aniline obtained in the previous step was transformed to the diazonium salt by treatment with isoamyl nitrite-H_2SO_4 in 98% ethanol. The diazonium salt obtained was converted to the title compound by heating in an aqueous sodium iodide solution. A yield of 58% was obtained in the transformation mp 102 - 103°. (lit.[57] 103°).

2,6-Dimethoxyiodobenzene

Lithium metal (2.3 g, 0.33 moles) and ether (150 ml) was placed in an oven-dried 500 ml 3-neck round bottom flask, fitted with a reflux condenser, dropping funnel and glass-covered magnetic bar. An atmosphere of nitrogen was maintained throughout the reaction. A solution of dry bromobenzene (47.1 g, 0.3 moles) in ether (100 ml) was slowly added. An exothermic reaction ensued and the rate of addition was adjusted so as to maintain a gentle reflux (one hour). The mixture was refluxed 1.5 hours longer and then filtered through an L-shaped tube with a cotton-glass plug, into a dry one liter 3-neck flask. To the murky solution, 1,3-dimethoxybenzene (0.25 moles) was added and the mixture left at room temperature for 72 hours. At this stage large clear crystals of 2,6-dimethoxylithiobenzene had been formed. A solution of iodine (0.25 moles) in ether (300 ml) was added dropwise, with stirring at a rate as to maintain reflux (one hour). The solution was refluxed three hours and then quenched by addition of water:H_2SO_4 (150 ml:2 ml). The layers were separated and the aqueous layer extracted with ether (100 ml). The ether extracts were combined and washed successively with water (100 ml), 5% sodium thiosulphate (2 x 80 ml), water (100 ml) and brine (80 ml). The dried ($MgSO_4$) solvent was removed under vacuum. A crystalline mass mixed with a dark oil was obtained. Skelly B was added (100 ml) and the crystals filtered. Recrystallization from

ethanol yields 50 g (70.5%) of beige-coloured 2,6-dimethoxy-iodobenzene mp 102°. (lit[59] 103°).

7-Methyl-1,4-dioxaspiro[4.4]nonane-7-acetaldehyde 51a

Chlorine (1 ml, 1.557 g, 22 mmoles) was condensed in a graduated pipet. This was then distilled, under nitrogen, into dry CH_2Cl_2 (P_2O_5) at -45° (CH_3CN-dry ice). To this solution, a mixture of DMSO (7 ml) in dry CH_2Cl_2 (5 ml), was added with vigorous mechanical stirring. The yellow colour of chlorine was discharged and a white precipitate formed. A solution of 7-methyl-1,4-dioxaspiro[4.4]nonane-7-ethanol (1 g, 5.38 mmole) in CH_2Cl_2 (5 ml) was added in one portion.

After vigorously stirring the slurry for 2.5 hours, the cooling bath was removed and triethylamine (5.5 ml) dissolved in CH_2Cl_2 (5 ml) and Skelly B (30 ml) was added to the warm (room temperature) slurry and then the solid was filtered off. A yellow oil that contained DMSO was obtained after removal of the solvent. This oil was dissolved in Skelly B (150 ml) and washed with water (5 x 10 ml) and brine (20 ml). The dried ($MgSO_4$) solvent was removed leaving the title aldehyde (650 mg, 65%) as a clear oil n_D^{20} 1.4779.

ir$_{(liquid\ film)}$: 2720, 1725 cm^{-1} (aldehyde).

nmr: δ 10.01 (t, 1, J=3Hz, C$\underline{H}$O), 3.88 (s, 4, OC$\underline{H}_2$C$\underline{H}_2$O), 2.46(d, 1, J=3Hz, C$\underline{H}_2$CHO), 2.14 - 1.47 (m, 6, ring methylenes) 1.19 (s, 3, C$\underline{H}_3$).

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.97, H, 8.94.

Dimethone derivative mp 133 - 134°.

Anal. Calcd. for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58; MW 446. Found: C, 69.77, 69.94; H, 8.61, 8.54; MW 446 (ms).

DMSO-Cl_2 oxidation of 2,8,8-trimethyl-6,10-dioxaspiro[4.5] decane-2-ethanol 63

The method of oxidation described previously using DMSO-Cl_2 complex and triethylamine was employed on the title alcohol (1.14 g, 5 mmoles) using the same proportions of reagents. The crude product (1.35 g) was percolated through silica gel M (100 g) packed in a 30 mm inner diameter column using Skelly B as solvent. The column was eluted successively with Skelly B (250 ml), Skelly B:Et_2O, 95:5 (500 ml) and Skelly B:Et_2O, 1:1 (1000 ml). Fractions of 150 ml were collected. Fractions 7 and 8 yield almost pure 67, 410 mg (36%).

ir$_{(liquid\ film)}$: 1750 cm^{-1} (cyclopentanone).

nmr: δ 4.67 - 4.43 (m, 1, O-C-C<u>H</u>-CO), 3.78 - 3.25 (m, 4, O<u>CH_2</u>C<u>CH_2</u>O), 2.5 - 1.5 (m, 8, 4 methylenes), 1.19 (s, 3, <u>CH_3</u>), 1.12 (s, 3, <u>CH_3</u>), 0.73 (s, 3, <u>CH_3</u>).

mass spectrum: m/e 226.1564 calcd. for $C_{13}H_{22}O_3$, 226.1569 meas. (6), 141(14), 97(36), 81(10), 69(66), 56(29), 55(23), 45(17).

Attempted DIBAL reduction of methyl 2,8,8-trimethyl-dioxaspiro[4.5]decane-2-acetate 59

To a cooled (-70°, dry ice-acetone bath) solution of the title compound (1.07 g, 4.18 mmoles) in dry toluene (Na-distilled), a solution of diisobutyl aluminum hydride (0.8 ml, 4.5 mmoles) in toluene (5 ml), was added dropwise under nitrogen, at such a rate as to maintain the temperature below -65°. After this addition was completed (20 minutes), methanol (2 ml) was added dropwise and the mixture allowed to warm to room temperature. The addition of saturated NH_4Cl (3 ml) formed a thick gelatin. After addition of ether (50 ml) the layers were separated and the aqueous layer extracted with ether (2 x 10 ml). The ethereal extracts were combined and washed in turn with water (2 x 20 ml) and brine (20 ml). The dried ($MgSO_4$) solvent was removed leaving 800 mg of a faintly yellow liquid.

ir (liquid film): 3420 cm^{-1} (OH), 2720 and 1725 cm^{-1} (CHO), 1735 cm^{-1} inflexion of 1725 cm^{-1} (ester).

nmr: δ 3.68 (s) and 1.13 (s) $COOCH_3$ and CH_3 of ester; 3.72 (t, J=7.5 Hz), and 1.04 (s) CH_2OH and CH_3 of alcohol, 2.43 (d, J=3 Hz), and 1.16 (s) CH_2CHO and CH_3 of aldehyde. Ratio of aldehyde, alcohol and ester, 5:2:3.

2,8,8-Trimethyl-6,10-dioxaspiro[4.5]decane-2-acetaldehyde 64

The chromium trioxide used in the oxidation was dried overnight in a vacuum desiccator (P_2O_5). The pyridine was refluxed over and distilled from barium oxide.

Chromium trioxide (6.0 g, 60 mmoles) was added to a mechanically stirred solution of pyridine (9.49 g, 120 mmoles) in dry CH_2Cl_2(P_2O_5). A deep-orange solution was obtained after all of the CrO_3 had dissolved (15 minutes). 2,8,8-Trimethyl-6,10-dioxaspiro[4.5]decane-2-ethanol (2.28 g, 10 mmoles) dissolved in CH_2Cl_2 (10 ml) was added in one portion. A black tarry precipitate separated immediately after addition. After 30 minutes of stirring the mixture was decanted and the tarry material washed with ether (3 x 20 ml). CH_2Cl_2 and ethereal washings were combined and the solvent removed under vacuum. The dark material obtained was taken up in ether (300 ml) and the ether was washed with $NaHCO_3$ until it no longer had a rusty colour. The dried (brine, $MgSO_4$) solvent was removed to obtain a liquid that contained pyridine. The pyridine was removed by adding benzene to the mixture and evaporating under vacuum (4 x 10 ml). In this way a slightly green liquid was obtained (1.857 g, 82%). The colour can be removed by quick percolation through a small amount of silica gel. The crude aldehyde however is sufficiently pure to be used without further purification. $ir_{(liquid\ film)}$: 2720 and 1725 cm^{-1} (CHO).

nmr: δ 9.82 (t, 1, J=3Hz, C$\underline{H}$O), 3.5 (s, 4, OC$\underline{H}_2$CC$\underline{H}_2$O), 2.47 (d, 2, J=3Hz, C$\underline{H}_2$CHO), 2.15 - 1.40 (m, 6, ring C$\underline{H}_2$'s), 1.19 (s, 3, C$\underline{H}_3$), 0.98 (s, 6, 2C$\underline{H}_3$).

Dimethone derivative mp 127°.

Anal. Calcd. for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08; MW 488.

Found: C, 71.62; H, 9.27; MW 488 (ms).

2-[2,6-Dimethoxyphenyl)ethyl]-2,8,8-trimethyl-6,10-dioxaspiro [4.5]decane 65

The magnesium turnings used for the Grignard reaction were surface-cleaned by repeated washings with 10% HCl and water, then dried by successive rinsing with ethanol and ether. Previous to use they were crushed in a mortar.

A mixture of 2,6-dimethoxyiodobenzene (7.14 g, 27 mmoles), magnesium turnings (850 mg, 35 mmoles) and a trace of iodine in dry THF (150 ml) was refluxed under nitrogen for 90 minutes. To the cool (room temperature) solution, 2,8,8-trimethyl-6,10-dioxaspiro[4.5]decane-2-acetaldehyde (5.52 g, 24.4 mmoles) dissolved in THF (10 ml) was added dropwise (5 minutes). The reaction mixture was then refluxed for 30 minutes. After cooling, saturated NH_4Cl was added (30 ml) followed by ether (500 ml). The aqueous layer was separated and washed with water and brine. A thick oil (9.14 g) was obtained after removal of solvent. The oil was placed on an alumina dry column (2" in diameter x 17" length)

and eluted with CH_2Cl_2. The column was divided into 10 portions (1 to 10 from top to bottom), and the fractions were eluted with CH_2Cl_2:MeOH. Fractions 2 to 7 were combined to obtain the alcohol (5.35 g, 55%) as a colourless, very thick oil.

ir$_{(liquid\ film)}$: 3650 (OH), 1600 and 1480 (aromatic), 778 and 720 cm^{-1} (1,2,3-substituted benzene).

nmr: δ 7.5 (q, 1, para H), 6.77 (d, 2, meta H), 5.8 - 5.3 (broad m, benzylic CH), 3.97 (s, 6, $2OCH_3$), 3.58 (broad m, 4, OCH_2CCH_2O), 2.2 - 1.3 (m, 8, methylenes), 1.22, 1.04, 0.97 and 0.94 (four singlets corresponding to 9H, $4CH_3$).

mass spectrum: m/e 364(3), 183(6), 169(6), 168(7), 167(100), 141(19), 137(7), 128(6), 112(8), 107(6), 97(9), 69(27), 56(7), 55(18), 43(6), 41(15).

2-[2-(2,6-Dimethoxyphenyl)ethyl]-2,8,8-trimethyl-6,10-dioxaspiro[4.5]decane 70

A solution of the benzylic alcohol 65 (470 mg, 1.3 mmoles) in absolute ethanol (610 mg, 0.8 ml, 7.8 mmol) and dry ether (1.5 ml), was added dropwise to 20 ml of sodium-distilled ammonia (later experiments showed this precaution to be unnecessary). To this solution, sodium (200 mg, 8.7 mmoles) cut in small pieces was added during 10 minutes. After 75 minutes, the reaction was quenched by dropwise addition of ethanol. The ammonia was rapidly evaporated by warming the solution in a water-bath,

the residue was treated with water (40 ml) and worked-up as in the previous experiment. The title compound was obtained as a thick yellowish oil which solidified while standing in the fridge. A yield of 445 mg (98%) was obtained. The yields were lower when the reaction was carried out on a larger scale (89 - 95%). An analytical sample was prepared by bulb to bulb distillation 200°/0.1 mm mp 37 - 38°.

ir: 1600 (aromatic), 770 and 715 cm^{-1} (1,2,3-substituted benzene).

nmr: δ 7.11 (q, 1) and 6.54 (d, 2) aromatic protons, 3.82 (s, 6, $2OCH_3$), 3.94 (s, 4, OCH_2CCH_2O), 2.66 (broad m, 2, benzylic protons), 2.2 - 1.3 (m, 8, $4CH_2$), 1.14, 1.00 and 0.95 (three s, 9, $3CH_3$).

mass spectrum: m/e 384(6), 183(57), 151(36), 141(44), 97(94), 96(19), 91(32), 69(70), 56(27), 55(66), 53(16), 43(24), 41(100), 39(48), 28(79).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.53; H, 9.23.

2,6-Dimethoxy-n-butylbenzene 68

A solution of 1-(2,6-dimethoxyphenyl)-1-butanol 59 in absolute ethanol (1.6 ml) and ether (4 ml) was added in one portion to sodium-distilled ammonia (50 ml). Sodium (1 g, 43.5 mmoles) cut in small pieces was added slowly (40 minutes). To this solution absolute ethanol was carefully added until the blue colour faded. The ammonia was

allowed to evaporate overnight and the white semi-solid left was taken up in water (60 ml). The aqueous solution was extracted with ether (4 x 20 ml) and the ethereal extracts washed in the usual way. The title compound was obtained as a colourless oil n_D^{20} 1.5127 (lit. n_D^{20} 1.5130).
ir corresponds to the reported data[59].
nmr: δ 7.1 (q, 1H), and 6.5 (t, 2) aromatic protons, 3.77 (s, 6, $2OC\underline{H}_3$), 2.65 (broad t, 2, benzylic $C\underline{H}_2$), 1.6 - 0.8 (m, 7, $C\underline{H}_2C\underline{H}_2C\underline{H}_3$).

Catalytic reduction of 2-methylresorcinol to 2-methyl-1,3-cyclohexanedione.

A solution of 2-methylresorcinol (6.2 g, 0.05 moles) in aqueous sodium hydroxide (2.2 g, 0.055 moles) was hydrogenated in a Parr hydrogenator at 50 psi for 17 hours using 0.55 g of 5% rhodium alumina as the catalyst. The slurry was filtered and cooled (0°). Concentrated HCl was added until the solution was acidic (pH 1), the solid that formed was filtered, air dried (20 minutes) and recrystallized from 95% EtOH (25 ml). The yellowish solid that was obtained (3.95 g, 64%) mp 204 - 206° proved to be identical (ir, nmr, tlc) with a sample prepared by methylation of 1,3-cyclohexanedione.

1-(2,6-Dimethoxyphenyl)-2-butene

The title compound was prepared by the method of Boltze, Dell and Jansen[59] in 40% yield (68% based on

recovered starting material) bp 76 - 80°/0.3 (lit. bp 106 - 108.5°/2 mm) n_D^{20} 1.5314 (lit. n_D^{20} 1.5319.
ir: fits described spectra.
nmr: δ 7.12 (q, 1) and 6.52 (d, 2), aromatic protons, 5.5 (m, 2, HC=CH), 3.8 (s, 6, 2 OCH_3), 3.35 (m, 2, $ArCH_2$ CH=CH), 1.57 (s, 3, CH_3).

Catalytic reduction of 1-(2,6-dimethoxyphenyl)-2-butene

A slurry of the title compound (19 g) and 5% palladium on charcoal catalyst (500 mg) was hydrogenated in a Parr hydrogenator at 50 psi for 30 minutes. The slurry was filtered and the solvent was removed to give a quantitative yield of 2,6-dimethoxy-n-butylbenzene, identical (ir, nmr, tlc) with a sample previously prepared.

Attempted Birch reduction of 2,6-dimethoxy-n-butylbenzene 68

A solution of the title compound (1.94 g) in dry THF (5 ml) and tert-butyl alcohol (5 ml) was added to ammonia (distilled over sodium, 50 ml). Lithium metal (300 mg) was added in small pieces (10 minutes) and the mixture stirred under reflux for five hours. The reaction was quenched by addition of tert-butyl alcohol. The ammonia was evaporated (water bath) and the residue worked-up in the usual way. The liquid obtained (1.85 g) was a mixture of starting material and dihydroaromatic compound 6:4.
$ir_{(liquid\ film)}$: 1600 cm^{-1} (aromatic), 1660 and 1695 cm^{-1}

vinyl ether).

nmr: δ 7.15 - 6.3 (m, aromatic protons), 4.7 (t, J=3.5Hz, vinyl proton), 3.77 (s, aromatic OCH_3), 3.55 (s, vinylic OCH_3).

Attempted modified Birch reduction of 2,6-dimethoxy-n-butylbenzene 68

Lithium metal (100 mg) was added to a mixture of the aromatic compound 68 in tert-butyl alcohol (1.4 ml) and n-propylamine (10 ml) and the slurry stirred at room temperature (4 hours). Additional lithium (100 mg) and tert-butyl alcohol (1.4 ml) were added and the stirring was continued for five hours. After removal of the solvent the residue was partitioned between ether and water. The ethereal portion was dried ($MgSO_4$) and the solvent removed to give 590 mg of a 65:35 mixture of starting material and dihydroaromatic compound. Its ir and nmr were similar to those reported previously.

2-n-Butylresorcinol 74

A mixture of 2,6-dimethoxy-n-butylbenzene (500 mg), glacial acetic acid (3 ml) and 48% HBr (3 ml), was refluxed for eight hours under nitrogen. The mixture was diluted with water (30 ml) and extracted with ether (4 x 10 ml). The ethereal extracts were washed with saturated $NaHCO_3$ (2 x 10

ml), water (10 ml) and brine. An orange semi-solid (250 mg) was obtained after removal of the solvent. This material was chromatographed on alumina (7 g) to obtain 180 mg (42%) of 2-n-butylresorcinol mp 79 - 80° (lit.[106] mp 83°).

ir$_{(CHCl_3)}$: 3580 (OH), 1600 cm^{-1} (aromatic).

nmr: δ 7.12 - 6.8 (q, 1, ArH), 6.5 - 6.3 (t, 2, ArH), 4.93 (s, 2, OH), 2.8 - 2.5 (broad t, 2, $ArCH_2$), 1.75 - 0.8 (m, 7, $CH_2CH_2CH_3$).

Treatment of 2,6-dimethoxy-n-butylbenzene with methylmagnesium iodide

The ether (500 mg, 2.6 mmoles) was mixed with 3 ml of a 3M solution of methylmagnesium iodide in ether. The solvent was removed by maintaining the mixture at 70°/2mm for one hour. The vacuum was removed and the mixture flushed with nitrogen. The nitrogen atmosphere was maintained while the mixture was immersed and kept for seven hours in an oil bath at 180°. The reaction mixture was cooled and EtOAc (1 ml) added followed by 30 ml of saturated NH_4Cl. The aqeuous mixture was extracted with ether (3 x 15 ml). The ethereal extracts were washed with brine and dried ($MgSO_4$). After solvent removal there remained 480 mg of a clear yellow oil. This was triturated with pentane leaving 410 mg (95%) of 2-n-butylresorcinol identical with a previously prepared sample.

Treatment of 2,6-dimethoxy-n-butylbenzene with pyridinium hydrochloride

A mixture of pyridinium hydrochloride (12 mg) and 2,6-dimethoxy-n-butylbenzene (1 g) was refluxed (Wood's metal bath, 230°) under nitrogen for three hours. The cool semi-solid was dissolved in water (60 ml) and the aqueous solution was extracted with ether (4 x 15 ml). The ethereal extracts were washed in turn with 10% HCl (3 x 10 ml) and brine (20 ml). The dried ($MgSO_4$) solvent was removed to yield an orange-brown oil (980 mg) that solidified upon scratching. Sublimation (60°/0.1mm) of the crude material yielded 2-n-butylresorcinol (720 mg, 86%) identical with a sample previously prepared.

Bis(2-tetrahydropyranyl)resorcinol

The title compound was prepared as described by Parham and Anderson[81]. Distillation, however, could not be accomplished owing to decomposition. Instead, the reaction mixture was diluted with ether, washed with cold 10% NaOH and brine and dried ($MgSO_4$). The bulk of the solvent and unreacted dihydropuran were removed under vacuum. This material was then left under vacuum overnight and used without distillation.

Bis(2-tetrahydropyranyl)-2-iodoresorcinol 77

A solution of PhLi (0.25 moles) in ether (200 ml) was prepared as already described. To this solution bis(2-tetrahydropyranyl)resorcinol (69.5 g, 0.25 moles) in ether (100 ml) was added dropwise under nitrogen. The mixture was left for 72 hours at room temperature. A solution of iodine (0.20 moles) was added dropwise; the resulting mixture was refluxed for three hours and then quenched by addition of water (200 ml). The layers were separated and the ethereal layer was in turn washed with 10% sodium thiosulphate (50 ml), water (50 ml) and brine. A thick orange oil was obtained after removal of solvent. Some crystallization took place when the oil was left under vacuum for two hours; trituration with pentane left a light-yellow solid (32 g, 38%). The solid is unstable, when left exposed at room temperature it changes into a thick brown oil.

ir$_{(CHCl_3)}$: 3040 - 3020 (aromatic), 1585 cm^{-1} (aromatic).

nmr: δ 7.38 - 7.05 (m, 1, Ar$\underline{H}$), 6.96 - 6.64 (m, 2, Ar$\underline{H}$), 5.5 (broad s, 2, 2 OC$\underline{H}$O), 4.15 - 3.35 (m, 4, 2 OC$\underline{H}_2$), 2.3 - 1.4 (m, 12, rest of C$\underline{H}_2$'s).

Reaction of 2,8,8-trimethyl-6,10-dioxaspiro[4.5]decane-2-acetaldehyde 64 with bis(2-tetrahydropyranyl)-2-lithioresorcinol 75

To a cooled (-70°) solution of bis(2-tetrahydro-

pyranyl)resorcinol (1.946 g, 7 mmoles) in ether (15 ml), n-butyllithium in hexane (1.5M, 5 ml) was added, under nitrogen, with stirring. The cooling bath was removed and the solution kept at room temperature for 16 hours. A solution of the aldehyde (1.356 g, 6 mmoles) in ether (5 ml) was added dropwise with stirring. Water (10 ml) was added carefully after three hours and the mixture stirred for five minutes. After having added ether (40 ml), the layers were separated and the ethereal phase was washed and dried as usual. Removal of the solvent left 2.896 g of a yellowish oil that was chromatographed on alumina (150 g, BDH). The column was successively eluted with Skelly B:benzene 9:1 (2 liters), Skelly B:benzene 7:3 (1 liter), and Skelly B:benzene 1:1. The latter eluted 2-[2-(1,5-ditetrahydropyran-2'-yloxyphenyl)-2-hydroxyethyl]-2-8,8-trimethyl-6,10-dioxaspiro[4.5]decane 76 (784 mg, 26%) as a very thick transparent oil.

$ir_{(liquid\ film)}$: 3550 (sharp OH), 1595 cm^{-1} (aromatic)

nmr: δ 7.36 - 6.65 (m, 3, ArH), 5.6 - 5.3 (m, 2, OCHO), 1.22, 0.98, 0.95 and 0.91 (four s, 9, CH_3).

mass spectrum: m/e 504.3087 calcd. for $C_{29}H_{44}O_7$, 504.3103 meas. (1), 335(3), 318(7), 188(4), 183(21), 141(5), 128(4), 123(4), 97(13), 86(6), 85(100), 69(16), 67(11), 57(19), 56(6), 55(16), 43(18), 41(28).

2-[2-(2,6-ditetrahydropyran-2'-yloxyphenyl)-2-hydroxyethyl]-2,8,8-trimethyl-6,10-dioxaspiro[4.5]decane 76

A solution of PhLi (0.1 moles) in ether (200 ml) was prepared as indicated previously. The solution was filtered, in a dry box, into an oven-dried 500 ml 3-neck round bottom flask fitted with condenser, dropping funnel and glass covered magnetic bar. A dry-nitrogen atmosphere was maintained throughout the reaction. To the clear solution, bis(2-tetrahydropyranyl)resorcinol (27.8 g, 0.1 moles) in ether (100 ml) was added and the solution was kept at room temperature for 60 hours. After some of the solvent was removed by distillation and the mixture was cooled, white crystals of the organolithium 75 separated. The bulk of the mother liquor was removed with an hypodermic syringe, dry ether was added (50 ml) and removed to rinse the crystals. Finally, ether was added (200 ml) and the mixture slurried. Freshly prepared aldehyde 64 (4.975 g, 22 mmoles) in ether (20 ml) was added dropwise to the slurry which was then stirred for 3.5 hours before quenching with saturated NH_4Cl (30 ml). The layers were separated and the ether layer was washed and dried in the usual manner. The oil obtained after removal of the solvent was chromatographed on alumina (1 Kg, BDH) as described previously. The desired alcohol 76 was obtained in 79% yield (based on aldehyde). It was identical (ir, tlc) with a sample prepared previously.

3-Methyl-3-[2-(2,6-dihydroxyphenyl)ethyl]cyclopentanone 79

A solution of the benzylic alcohol 76 obtained in the preceding reaction (4.94 g) in ether (60 ml) was added to liquid ammonia (150 ml). To the solution, sodium (1.39 g) cut in small pieces, was added over five minutes. The mixture was stirred for 10 minutes and absolute ethanol was added dropwise until the blue colour of the ammoniacal solution faded. It was worked-up as in previous reactions to yield 2-[2-(2,6-ditetrahydropyran-2'-yloxyphenyl)ethyl]-2,8,8-trimethyl-6,10-dioxaspiro[4.5]decane 78 as a thick oil (4.25 g, 89%). A portion of this material (2.25 g) was dissolved in a mixture of 90% aqueous methanol (50 ml) and 5% aqueous oxalic acid (5 ml). After two hours at 50° the solution was cooled and diluted with water. The aqueous solution was extracted with ether and the ethereal extracts were dried ($MgSO_4$). The solvent was removed to leave a clear oil (1.83 g). The oil after trituration with Skelly B left 79 as a white solid (853 mg, 79%), recrystallized from Skellysolve B-Et_2O mp 166 - 167°.

ir$_{(CHCl_3)}$: 3360 (OH), 1745 cm^{-1} (C=O).

nmr: δ 6.92 - 6.7 (m, 1, ArH), 6.33 (d, 2, J=8Hz, ArH), 2.8 - 1.5 (m, 10, $5CH_2$), 1.19 (s, 3, CH_3).

mass spectrum: m/e 234 (3), 138(6), 123(29), 97(100), 77(9), 55(12), 41(21).

Anal. Calcd. for $C_{14}H_{18}O_3$; C, 71.77; H, 7.74. Found: C, 71.68; H, 7.71.

Catalytic reduction of 2-n-butylresorcinol

2-n-Butylresrocinol (83 mg, 0.5 mmoles) was placed in a 50 ml pressure polymer bottle together with 5% rhodium alumina catalyst (15 mg), 1N NaOH solution (0.55 ml) and a magnetic bar. The bottle was capped and hydrogen was introduced through an hypodermic needle attached to a pressure gauge. The container was flushed twice and the pressure was adjusted to 50 psi. The slurry was vigorously stirred for 18 hours at room temperature. After uncapping the bottle the mixture was neutralized (1N HCl, 0.55 ml) and extracted with ether (3 x 3 ml). Removal of the dry ($MgSO_4$) solvent gave a quantitative yield of crude 2-butyl-1,3-cyclohexanedione identical with an authentic sample of that material.

2-[2-(2,6-Dihydroxyphenyl)ethyl]-2,8,8-trimethyl-6,10-dioxaspiro[4.5]decane 80

A mixture of 3-methyl-3-[2-(2,6,dihydroxyphenyl) ethyl]cyclopentanone 79 (2.34 mg, 1 mmole), 2,2-dimethyl-1,3-propanediol (163 mg, 1.5 mmoles) and 2 mg of p-toluenesulphonic acid was dissolved in EtOAc (5 ml) and benzene (30 ml). The solution was heated under reflux with azeotropic removal of water for 24 hours. More alcohol (102 mg, 1 mmole) was added to the solution and reflux was continued for 16 hours longer. To the cool solution, solid Na_2CO_3 (30 mg) was added and the slurry was stirred for ten minutes.

After filtration and evaporation of the solvent, the brown oil obtained was chromatographed on alumina (40 g). The column was eluted successively with CH_2Cl_2 (16 fractions, 20 ml) and EtOAc, (20 ml fractions). Fractions 19 - 23 contained 280 mg (87%) of nearly pure ketal 80 as a dark yellow oil.

ir$_{(\text{liquid film})}$: 3350 (broad, OH), 1605 cm^{-1} (aromatic).

nmr: δ 7.1 - 6.7 (t, 1, ArH), 6.5 - 6.3 (d, 2, ArH), 5.68 (broad s, 2 OH), 3.5 (s, 4, OCH_2CCH_2O), 2.9 - 1.3 (m, 10, CH_2 's), 1.16, 1.07 and 0.95 (three s, 9, 3 CH_3).

This product is not stable and slowly reverts to starting material. It was used in the next step without further characterization.

2-[2-(2,6-Dioxocyclohexyl)ethyl[-2,8,8-trimethyl-6,10-dioxaspiro[4.5]decane 81

The hydrogenation of the resorcinol prepared on the previous step, 80 (280 mg) was carried out in the same way as that of 2-n-butylresorcinol. After extraction with ether, the corresponding 1,3-cyclohexanedione 81 was left as a thick oil (270 mg, 96%) that solidified on standing.

ir$_{(CHCl_3)}$: 3610 and 3360 (enol). 1740 (shoulder), 1705 and 1610 cm^{-1} (1,d-cyclohexanedione.

nmr: δ 3.43 (broad s, 4, OCH_2CCH_2O), 1.02 (s, 3, CH_3), 0.94 (s, 3, CH_3), 0.88 (s, 3, CH_3),

mass spectrum: m/e 322.2144 calcd. for $C_{19}H_{30}O_4$, 322.2156 meas. (4), 183(47), 141(92), 97(89), 69(96), 56(33), 55(100).

Acid catalyzed cyclization of 3-methyl-3-[2-(2,6-dioxocyclohexyl)ethyl]cyclopentanone 82

A 20 mg portion of the 1,3-cyclohexanedione 81 was stirred for one hour in dilute H_3PO_4 (3 ml). Ether extraction gave 11 mg of the corresponding triketone 82. This material was dissolved in $CHCl_3$ (3 ml) containing a trace of p-toluenesulphonic acid, and the solution was refluxed under nitrogen for 26 hours. To the cool mixture solid Na_2CO_3 was added with stirring (5 minutes). A red-brown oil (8 mg) was left after the Na_2CO_3 and solvent were removed. The material was separated on a 10 x 25 cm silica gel plate (0.25 mm thickness) by elution with $CHCl_3$:CH_3OH, 95:5. A wide yellow band (R_f 0.7) was divided in three parts and scraped. The three portions were eluted with ether to give, 1 mg, 2 mg, and 1 mg, high, medium and low bands respectively. The spectral data of the compound with lowest R_f is consistent with 3a-methyl-2,3,4,5,5a,7,8,9-octahydro-1H-benz[e]indene-1,6-dione 83.

ir$_{(CCL_4)}$: 1730 cm^{-1} and 1715 cm^{-1} (shoulder).

mass spectrum: m/e 218(36), 163(42), 161(38), 97(46), 91(51), 69(60), 57(59), 55(100).

Attempted methylation of 2-[2-(2,6-dioxocyclohexyl)ethyl]-2,8,8-trimethyl-6,10-dioxaspirodecane 81

To a methanolic (0.1 ml) solution of the dione 81 (6.5 mg) and Triton B (40% CH_3OH solution, 0.2 ml), methyl

iodide (5 mg) was added and the mixture was refluxed under nitrogen for three hours. After having added more methyl iodide (5 mg), the solution was refluxed for 14 hours. Water was added (5 ml) and the resulting aqueous solution was extracted with ether (3 x 2 ml). The dried ($MgSO_4$) ether was removed leaving an orange oil (4 mg).

ir$_{(1\%\ CCl_4)}$: 1740 (ester), 1715 cm^{-1} (ketone).

mass spectrum: m/e 368(2), 183(100), 141(82), 97(87), 69(97), 57(65), 55(82).

2-[2-Hydroxy-(2-methoxyphenyl)ethyl]-2,8,8-trimethyl-6,10-dioxaspiro[4.5]decane 86

An oven-dried 500 ml 3-neck round bottom flask fitted with reflux condenser, dropping funnel and magnetic bar was used in this preparation. A dry nitrogen atmosphere was maintained. Surface-cleaned magnesium turnings (824 mg, 34 mmoles), o-iodoanisole (7.02 g, 30 mmoles) and iodine (10 mg) were refluxed for one hour in dry ether (200 ml). To the resulting solution, 2,8,8-trimethyl-6,10-dioxaspiro-[4.5]decane-2-acetaldehyde 64 (6.2 g, 27.4 mmoles) in ether (20 ml) was added dropwise (10 minutes) and the mixture refluxed for 20 minutes. The cool solution was treated with saturated NH_4Cl (100 ml) and the layers were separated. The aqueous layer was extracted with ether (3 x 20 ml) and the combined ethereal extracts were washed and dried in the usual manner. The oil that was obtained (9.73 g) was chromatographed

on alumina (500 g, BDH). The column was eluted in turn with Skelly B:Et_2O, 95:5 (2 liters; fractions 1 - 11, 180 ml) and Skelly B:Et_2O, 1:1 (3 liters; fractions 12 - 24, 60 ml); fractions 24 - 36, 200 ml). From fractions 4 and 5 2-[2-(2-methoxypheny1)ethy1]-2,8,8-trimethy1-6,10-dioxaspiro[4.5]-decane 87 was obtained in 2% yield (characterization described later). The benzylic alcohol 86 was obtained (3.81 g, 42%) from fractions 22 - 29.

ir$_{(\text{liquid film})}$: 3550 (OH), 1605 and 1590 (aromatic), 755 cm^{-1} (1,2-substituted benzene).

nmr: δ 7.5 (m, 4, Ar$\underline{H}$), 5.06 (broad t, 1, C$\underline{H}$Ar), 3.77 (s, 3, OC$\underline{H}_3$), 3.5 - 3.32 (m, 4, OC$\underline{H}_2$CC$\underline{H}_2$O), 2.73 (broad s, 1, O$\underline{H}$), 2.14 - 1.5 (m, 8, 4 C$\underline{H}_2$), 1.16 and 1.13 (two s, 3, C$\underline{H}_3$), 0.95 (s, 6, 2 C$\underline{H}_3$).

mass spectrum: m/e 334.2144 calcd. for $C_{20}H_{30}O_4$, 334.2153 meas. (7), 198(23), 183(25), 169(20), 141(98), 137(72), 134(49), 121(19), 115(24), 108(24), 97(48), 91(21), 77(21), 69(100), 56(34), 55(83).

Using the same procedure with tetrahydrofuran as solvent, a higher yield (55%) of 86 was obtained.

2-[2-(Methoxyphenyl)ethyl]-2,8,8-trimethyl-6,10-dioxaspiro-[4.5]decane 87

The benzylic alcohol 86 (766 mg) dissolved in absolute ethanol (10.4 ml) and ether (4 ml) was added to liquid ammonia. Sodium metal (150 mg) was added rapidly to

the solution. After five minutes of stirring the reaction was quenched by addition of ethanol (0,5 ml). Work-up in the usual manner gave 87 as a clear oil (722 mg, 98%).

ir$_{(liquid\ film)}$: 1605, 1590 (aromatic), 755 cm^{-1} (1,2-substituted benzene).

nmr: δ 7.34 - 6.67 (m, 4, ArH), 3.77 (s, 3, OCH_3), 3.45 (s, 4, OCH_2CH_2O), 2.8 - 2.4 (m, 2, CH_2Ar), 2.2 - 1.38 (m, 8, CH_2's), 1.11, 0.98 and 0.93 (three 3, 0, 3 CH_3).

mass spectrum: m/e 318(8), 184(11), 183(94), 169(12), 141(66), 121(49), 97(70), 83(10), 79(10), 77(14), 69(100), 57(10), 56(22), 45(11).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.48, 75.52; H, 9.76, 9.76.

3-Methyl-3-[2-(1-oxo-2-cyclohexen-6-yl)ethyl]cyclopentanone 89

To liquid ammonia (20 ml) was added a solution of the aromatic compound 87 (318 mg) in ether (5 ml) and absolute ethanol (1 ml). The reaction mixture was stirred vigorously for one hour and quenched by addition of absolute ethanol. Work-up in the usual way gave a mixture of aromatic and dihydroaromatic compounds (290 mg). The mixture was treated with 1:1 hydrochloric acid, water for 16 hours. The mixture obtained after ether extraction was chromatographed on alumina (40 g). Elution with ether gave 67 mg (30%) of 89 contaminated with a compound of similar polarity.

ir$_{(CCl_4)}$: 1745 (cyclopentanone), 1685 cm^{-1} (α,β-unsaturated ketone).

nmr: δ 6.97 (d of t, 1, J=10, 4Hz, O=C-CH=C<u>H</u>), 5.98 (d of t, 1, J=10, 2Hz, O=C-C<u>H</u>), 1.08 (s, 3, C<u>H</u>$_3$).
mass spectrum: <u>m/e</u> 220(47), 147(46), 118(39), 105(44), 97(45), 91(68), 79(44), 77(48), 67(33), 55(62), 43(49), 41(100).

3-Methyl-3-[2-(1-oxo-3-cyclohex-6-yl)ethyl]cyclopentanone <u>91</u>

To ammonia (140 ml), 2-[2-(2-methoxyphenyl)ethyl]-2,8,8-trimethyl-6,10-dioxaspiro[4.5]decane <u>87</u> (2 g) was added dissolved in ether (30 ml) and absolute ethanol (15.12 ml). Sodium (7.2 g) was then added slowly (40 minutes). The solution was stirred for two hours after addition was completed, then ethanol was added dropwise until the sodium was destroyed. The resulting mixture was taken up in water (500 ml) and the resulting aqueous solution was extracted with ether. The dried ($MgSO_4$) ethereal extracts gave a clear oil that showed no aromatic absorption in the ir. The crude dihydro-aromatic compound was stirred for 90 minutes at room temperature in a mixture of methanol (50 ml) and water (10 ml) containing oxalic acid (100 mg). The reaction mixture was then diluted with water (100 ml) and extracted with ether (4 x 20 ml) to afford 1.360 g of crude 3-methyl-3-[2-(1-oxo-3-cyclohexen-6-yl)ethyl]cyclopentanone <u>90</u> as a clear oil.
ir$_{(CCl_4)}$: 1745 (cyclopentanone), 1720 cm^{-1} (cyclohexanone).

The crude <u>90</u> was dissolved in ethanol (50 ml) and

hydrogenated at 50 psi in a Parr hydrogenator over 5% palladized charcoal (100 mg) for two hours. After removal of catalyst and solvent the title compound 91 was obtained as an oil (1.150 g).

ir$_{(CCl_4)}$: 1745 (cyclopentanone) 1715 cm^{-1} (cyclohexanone).

nmr: δ 1.09 (s, 3, CH_3).

mass spectrum: m/e 222(9), 125(6), 98(100), 97(54), 83(6), 81(5), 70(6), 69(16), 67(12), 55(31), 41(38).

9a-Hydroxy-3a-methyl-2,3,4,5,5a,6,7,8,9,9b-decahydro-1H-benz[e]indene-1-one 94

The crude 3-methyl-3-[2-(1-oxo-3-cyclohex-6,yl)-ethyl]cyclopentanone 91 obtained in the previous reaction was dissolved in MeOH (80 ml). To the solution, aqueous sodium hydroxide (1N, 15 ml) was added and the mixture kept under nitrogen for 100 minutes at room temperature. After the solution was neutralized (1N HCl, 15 ml), some of the methanol was removed under vacuum and the residue was diluted with water (150 ml). Extraction with ether (4 x 50 ml) left, after evaporation of the dried ($MgSO_4$) ethereal extracts, a white semi-solid. Recrystallization from Skelly B-Et_2O gave 455 mg (48% overall from Birch reduction) of colourless prisms mp 149 - 150°.

ir$_{(CCl_4)}$: 3615 (OH), 1740 cm^{-1} (cyclopentanone).

nmr: δ 0.92 (s, 3, CH_3).

mass spectrum: m/e 222.1620 calcd. for $C_{14}H_{22}O_2$, 222.1618

meas. (11), 194(9), 179(7), 149(12), 109(8), 98(100), 81(7), 67(7), 55(10).

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.41; H, 9.99.

Dehydration of 9a-hydroxy-3a-methyl-2,3,4,5,5a,6,7,8,9,9b-decahydro-1H-benz[e]indene-1-one 94

The ketol 94 (46 mg) was heated to reflux in a 10% aqueous potassium hydroxide solution for 20 hours under nitrogen. The solution was cooled and extracted with ether. A clear oil (36 mg) was obtained after evaporation of the dried ethereal extracts. The oil, a mixture of compounds, contains mainly 3a-methyl-2,3,4,5,6,7,8,9-octahydro-1H-benz[e]indene-1-one-95.

ir$_{(CCl_4)}$: 1745, 1715 (shoulder), 1635 cm^{-1} (C=C).

nmr: δ 1.11 (s, CH_3).

mass spectrum: m/e 204(88), 189(35), 148(51), 147(64), 121 121(24), 105(42), 97(100), 91(37), 55(23).

Attempted methylation of 3a-methyl-2,3,4,5,6,7,8,9-octahydro-1H-benz[e]indene-1-one 95

A solution of the ketone 95 (20 mg) in benzene (3 ml) was treated with a slight molar excess of potassium tert-amylate under nitrogen. An excess of methyl iodide was added and the mixture kept at 70° for three hours. The reaction mixture was neutralized with dilute hydrochloric

acid and partitioned between water and Skellysolve B. From the dried organic layer a dark oil (18 mg) was obtained.

ir$_{(CCl_4)}$: 1745, 1715 cm^{-1}.

mass spectrum: m/e high molecular ion peaks, 246, 232, 218, 204.

Attempted enol-acetate formation of 95

To a solution of the ketone 95 (20 mg) in carbon tetrachloride (1 ml), acetic anhydride (0.1 ml) and 50% perchloric acid (5 ml) were added. After 90 minutes the mixture was diluted with Skellysolve B and washed successively with saturated sodium bicarbonate solution and water. After removal of the dried solvent a dark oil was obtained (18 mg). After evaporation distillation a yellow oil (10 mg) was obtained. This material decomposes on standing.

ir$_{(CCl_4)}$: 1750 cm^{-1}.

nmr: δ 2.13 (s), 1.22 (s).

Preparation of dihydrocarvone[90]

To a one liter flask fitted with dropping funnel and reflux condenser was added zinc powder (85 mg), potassium hydroxide (35 g), water (135 ml) and 95% ethanol (350 ml). The mixture was heated to reflux and carvone* (64 g) dissolved in 95% ethanol (150 ml) was added with

* Both (-) and (+) carvone were used for these preparations.

vigorous stirring, over a period of six hours. After an hour, the cool mixture was filtered and most of the solvent was removed under vacuum. The residue was extracted with three 100 ml portions of petroleum ether. The organic layer was washed successively with dilute acetic acid and water. After removal of the dried solvent, dihydrocarvone was obtained by distillation bp 75°/4 mm. (84%) (lit.[90] bp 80°/6 mm). Its spectroscopic properties are consistent with those reported.

5β-Hydroxy-7β(H)-14-noreudesm-11-en-3-one

The procedure of D.W. Theobald[91] was followed. A mixture of 5β-hydroxy-7β(H)-14-noreudesm-11-en-3-one and 7β(H)-14-noreudesma-4,11-dien-3-one 98 (58% based on 49.6% recovered dihydrocarvone) was obtained after distillation bp 145 - 150°/ 1 mm (lit. 146 - 148°/0.5 mm).

$ir_{(liquid\ film)}$: 3440 (broad, OH), 1715 (saturated ketone), 1670 cm^{-1} (α,β-unsaturated ketone).

The intensities of saturated and unsaturated carbonyl absorption were approximately the same. No efforts to separate the mixture were made and it was used as such in the next step.

7β(H)-14-Noreudesma-4,11-dien-3-one 98

Two grams of the mixture obtained in the preceding reaction was refluxed under nitrogen (8 hours) in aqueous

10% potassium hydroxide (20 ml). The cooled mixture was extracted with ether to yield 1.82 g of crude 98.

ir$_{(liquid\ film)}$: 1678 (unsaturated ketone), 885 cm^{-1} (C=C$\underline{H}_2$).

nmr: δ 5.77 (s, 1, C4 $\underline{H}$), 4.9 - 4.7 (broad d, 2, C=C$\underline{H}_2$), 1.72 (s, 3, C$\underline{H}_3$-C=C), 1.26 (s, 3, C$\underline{H}_3$).

5β-Hydroxy-4β,7β(H)-eudesm-11-en-3-one 104

The title compound was prepared as described by Halsall, Theobald and Walshaw[89]. A slight modification in the procedure, dropwise addition of 1-chloropentan-3-one dissolved in an equal volume of dry THF while keeping the reaction mixture temperature at -20°, led to an improved yield of the ketol (82% based on recovered dihydrocarvone).

mp 105 - 106° (lit.[89] mp 108°).

ir$_{(CHCl_3)}$: 3610 (sharp) and 3450 (OH), 1715 (C=O), 1648 and 885 cm^{-1} (C=C$\underline{H}_2$).

7β(H)-Eudesma-4,11-dien-3-one 105

A mixture of the ketol 104 obtained in the above mentioned procedure (31 g) and 10% aqueous potassium hydroxide (500 ml) was refluxed under nitrogen for eight hours. Extraction of the cool solution with ether left an oil (28 g) that was distilled under reduced pressure. 7β(H)-Eudesma-4,11-dien-3-one 105 was obtained as a clear liquid bp 124°/0,6 mm (lit[89] bp 130°/0.5 mm). n_D^{20} 1.5328 (lit.[89]

n_D^{20} 1.5334,

ir (liquid film): 1675 (unsaturated ketone), 885 cm^{-1} ($C=C\underline{H}_2$).

nmr: δ 4.82 and 4.63 (two m, 2, $C=C\underline{H}_2$), 1.24 (s, 3, $C\underline{H}_3$).

7β(H)-4-Methyl-eudesma-5,11-dien-3-one 99

To a solution of 7β(H)-eudesma-4,11-dien-3-one 105 (11.6 g, 57.0 mmole) in dry THF (100 ml), potassium tert-amylate in benzene (1.08M, 50 ml) was added and the mixture was heated under nitrogen (60 - 70°) for 15 minutes. To the cooled solution (ice-water bath), methyl iodide (7.2 g), dry THF (72 ml) was added in one portion and the mixture was stirred at 0° for 30 minutes. After neutralizing the reaction with dilute acetic acid, the solvent was removed under vacuum. The residue was dissolved in ether (300 ml) and washed with water, saturated sodium bicarbonate, water and brine. A yellow oil (14.49 g) was obtained after removal of the dried (Na_2SO_4) solvent. A portion of the oil (6.79 g) was chromatographed on silicic acid (500 g) 7β(H)-4-methyl-eudesma-5,11-dien-3-one 99 (5.1 g) was obtained by elution with CH_2Cl_2.

ir (liquid film): 1715 (C=O), 1650 and 890 cm^{-1} ($C=C\underline{H}_2$).

nmr: δ 5.48 (d, 1, J=4Hz, $\underline{H}$-6), 4.82 and 4.62 (2m, 2, $C=C\underline{H}_2$), 2.86 - 2.41 (m, 3, double allylic $\underline{H}$ and C2 $\underline{H}$'s), 1.77 (s, 3, vinylic $C\underline{H}_3$), 1.27, 1.24 and 0.98 (three s, 9, $3C\underline{H}_3$). These values are consistent with those reported[107].

mass spectrum: 232(30), 147(33), 137(12), 135(12), 134(32), 133(100), 132(14), 131(12), 121(13), 119(22), 107(19), 105(26), 100(11), 93(16), 91(28), 79(14), 77(17), 55(18), 41(42).

Semicarbazone mp 183 - 185°.

Anal. Calcd. for $C_{17}H_{27}N_3O$: C, 70.55; H, 9.40.

Found: C, 70.83; H, 9.33.

Ozonolysis of 7β(H)-4-methyl-eudesma-5,11-dien-3-one 99

The title compound (1.180 g, 5 mmoles) in CH_2Cl_2 (5 ml), was added to 220 ml of ozone-saturated methylene chloride (5.5 mmoles of ozone) at -78°. The solution was left at this temperature for 20 minutes and then treated with aqueous acetic acid (1:2, v:v; 50 ml) and powdered zinc (500 mg). After the slurry was vigorously stirred at room temperature for 40 minutes, the CH_2Cl_2 was separated and washed with saturated sodium bicarbonate, water and brine. Evaporation of the solvent left an orange oil (1.17 g) that was chromatographed on silicic acid (100 g). Elution with CH_2Cl_2 afforded a white solid (450 mg, 38.5%) that corresponds to 12-nor-7β(H)-4-methyl-eudesma-5-en-3,11-dione 100 mp 67 - 68°.

$ir_{(CHCl_3)}$: 1710 (ketone), 1355 cm^{-1} (sharp, methyl of methyl ketone).

nmr: δ 5.72 (d, 1, J=4.5Hz, H-6), 3.22 - 2.9 (m, 1, C7 H), 2.19 (s, 3, CH_3CO), 1.26 (s, 6, 2 CH_3), 0.98 (s, 3, CH_3).

mass spectrum: m/e 234.1614 calcd. for $C_{15}H_{22}O_2$, 234.1620 meas. (10), 191(14), 190(100), 184(12), 149(11), 125(11), 121(14), 119(12), 107(26), 105(23), 97(13), 91(25), 81(16), 79(38), 77(16), 67(17), 55(15), 43(71), 41(37).
Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.75; H, 9.67.

OsO_4-$NaIO_4$ oxidation of 7β(H)-4-methyl-eudesma-5,11-dien-3-one 99

A mixture of the title compound (1.18 g, 5 mmoles) and osmium tetroxide (105 mg, 0.4 mmoles) in dioxane (40 ml) and water (15 ml) was stirred in the dark for 20 minutes. A solution of sodium periodate (3.45 g, 15.5 mmoles) in water (25 ml) was added and the resulting slurry was stirred for one hour. After water was added (250 ml), the aqueous solution was extracted with ether (4 x 70 ml) and the ethereal extracts were in turn washed with 10% sodium sulfide, water and brine. The dried (Na_2SO_4) solvent was removed leaving 900 mg (76%) of a dark oil that solidified on cooling. The ir is superimposable on that of the preceding sample.

Ozonolysis of 5β-hydroxy-4β,7β(H)-eudesm-11-en-3-one

Ozone was bubbled through a solution of the title ketol (247 mg) in CH_2Cl_2 (40 ml) at -78° until a blue colour developed. The mixture was then treated with

zinc dust (100 mg) and 2% AcOH (15 minutes) at room temperature. The phases were separated and the CH_2CL_2 was washed with saturated $NaHCO_3$, water and brine. The dried (Na_2SO_4) solvent was evaporated under vacuum. The diketone 12-nor-5β-hydroxy-4β,7β(H)-eudesm-3,11-dione 106 was obtained as a white solid (217 mg, 87%) mp 181 - 183° (lit.[99] 179 - 180°).

$ir_{(CHCl_3)}$: 3610, 3460 (OH), 1715 (C=O), 1355 cm^{-1} (CH_3CO).
nmr: δ 1.14 (s, 3, $C\underline{H}_3CO$), 1.25 (s, 3, ($C\underline{H}_3$), 1.0 (d, 3, J=7 Hz, secondary $C\underline{H}_3$).

7α(H)-12-noreudesm-4-en-3,11-dione 107

The ketol obtained in the preceding reaction (500 mg) was refluxed for one hour in THF (15 ml) and concentrated hydrochloric acid (50 ml). Ether was added (50 ml) and the solution washed with saturated $NaHCO_3$ and brine. After evaporation of the solvent an oil was obtained (400 mg) that solidified upon scratching. Recrystallization from Skelly B:Et_2O gave the pure dione as colourless prisms (321 mg, 70%) mp 77 - 78° (lit.[99] mp 77.5 - 78.1°).

$ir_{(CHCl_3)}$: 1715, 1680, 1615 cm^{-1}
nmr: δ 2.1 (s, 3, $CH_3C=O$), 1.65 (s, 3, $CH_3C=C$), 1.2 (s, 3, $C\underline{H}_3$).

1,4a-Dimethyl-3,4,4a,5,6,7,8-heptahydronaphthalen-2-one 110

A mixture of 2-methylcyclohexanone (56 g, 0.5

moles) and sodium hydride (24 g, 50% oil dispersion) in dry THF (250 ml) and ethanol (1 ml), was refluxed under nitrogen for 1.5 hours. The mixture was cooled to -20°. A solution of 1-chloro-3-pentanone (60 g) in THF (100 ml) was added dropwise (30 minutes). After addition was complete the mixture was stirred at room temperature for 10 hours. After work-up (as in previous similar procedures) the crude product was distilled. Two main fractions were collected: 36 - 60° /0.7 mm (14.1 g, 2-methylcyclohexanone) and 105 - 120°/0.7 mm (42 g). The latter fraction was refluxed for 1.5 hours in in 10% KOH and extracted with ether. The resulting oil (40.66 g) was distilled to give the decalone 110 in 56% yield (based on recovered 2-methylcyclohexanone) bp 104 - 106°/1.5 mm (lit.[101] bp 99 - 100°/1 mm).

ir$_{(\text{liquid film})}$: 1672 (α,β-unsaturated ketone), 1615 cm^{-1} (conjugated double bond).

nmr: δ 1.78 (s, 3, vinylic CH_3), 1.24 (s, 3, CH_3).

1,1,4a-Trimethyl-1,3,4,4a,5,6,7-heptahydronaphthalen-2-one 111

The methylation of the preceding decalone was carried out as described by Mukherjee and Dutta[101]. A Colourless liquid was obtained in 91% yield after distillation bp 107 - 112°/2 mm (lit.[107] 105 - 107°/2 mm). In our hands, however, a mixture was obtained consisting mainly of the desired decalone (85 - 90%) and possibly the 1,1,3,4a-

tetramethylated ketone (15 - 10%). GC separation using: column, 15% FFAP on 60/80 chromosorb W 10' x 3/8"; temperature 150°, flow rate 10 ml/7 second.

$ir_{(liquid\ film)}$: 1715 cm^{-1} (C=O).

nmr: δ 5.62 (t, 1, J=3.5Hz, C=C<u>H</u>), 1.23 (s, 6, 2 $C\underline{H}_3$), 0.99 (s, 3, $C\underline{H}_3$).

2,2-Dimethyl-1,3-propanediol acetal of 1,1,4a-trimethyl-1,3,4,4a,5,6,7-heptahydronaphthalen-2-one <u>114</u>

The mixture of ketones obtained in the last reaction (1.92 g), 2,2-dimethyl-1,3-propanediol (1.872 g, 20 mmol) and 10 mg of <u>p</u>-TSA was dissolved in benzene (50 ml). The solution was heated under reflux with azeotropic removal of water for 24 hours. The solvent was distilled and the residue triturated with Skellysolve B. The solid was filtered off (propanediol) and the filtrate was dissolved in THF (30 ml). To this solution 10 ml of 1.1M $LiAlH_4$ in ether was added. After stirring for one hour at room temperature, the reaction was worked-up (addition of water, 15% NaOH and water) to obtain a colourless oil (2.126 g). The oil was dissolved in pentane (5 ml) and left in the fridge overnight. Some crystallization took place, the white solid was recrystallized from CH_3OH to obtain 460 mg of colourless prisms. The pentane and methanol filtrates were combined and percolated through alumina (80 g) using Skellysolve B:acetone, 98:2. A further 600 mg of pure <u>114</u> were obtained. mp 75 - 76.5°.

ir$_{(CHCl_3)}$: 2950, 2930, 2870, 1475, 1115, 1085 cm^{-1}.
nmr: δ 5.58 (t, 1, C-C<u>H</u>), 3.95 - 3.20 (m, 4, OC<u>H$_2$</u>CC<u>H$_2$</u>O), 1.24, 1.22, 1.18, 1.14 and 0.72 (five s, 15, 5 C<u>H$_3$</u>).
mass spectrum: 278.2246 calcd. for $C_{18}H_{30}O_2$, 278.2259 meas. (2), 142(11), 141(100), 69(13), 55(41), 41(18),
Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.36; H, 10.94.

Diels-Alder reaction of 4-cyclopentene-1,3-dione with 1-vinylcycloheptene

A mixture of 4-cyclopentene-1,3-dione (96 mg) and 1-vinylcycloheptene[108] (134 mg) in ether (5 ml) was left at 0° for 48 hours. The solid which formed was filtered off to give 117 mg (56%) of the Diels-Alder adduct <u>115</u> mp 187 - 190°.
ir$_{(KBr)}$: 1590 cm^{-1} (carbonyl).
nmr$_{(DMSO\text{-}d_6)}$: δ 5.98 (broad s, 1, <u>H</u>C=C).
mass spectrum: 218.1307 calcd. for $C_{14}H_{18}O_2$, 218.1314 meas. (32), 176(39), 175(12), 158(24), 133(14), 121(16), 105(23), 98(14), 93(22), 92(38), 91(100), 79(36), 77(20), 67(14), 65(11), 41(40).

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PART II: AN INVESTIGATION OF SOME INTRAMOLECULAR DIELS-ALDER REACTIONS

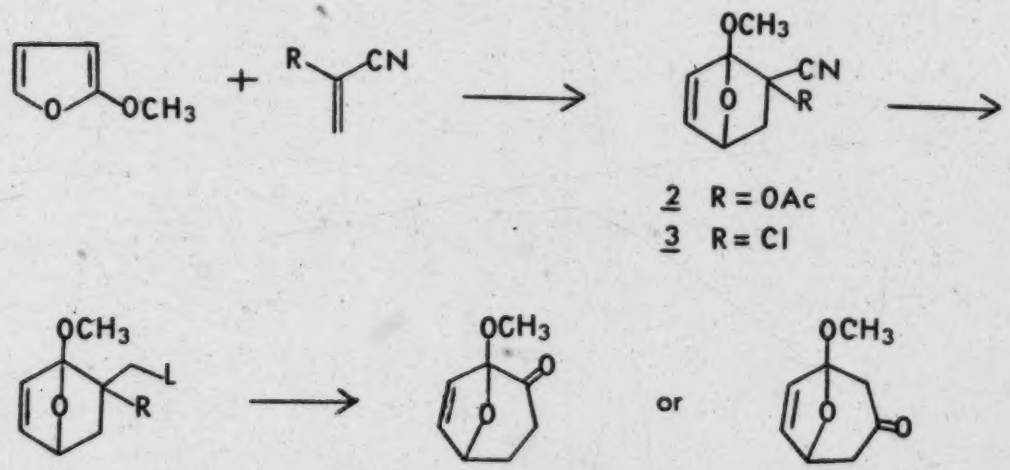
DISCUSSION

Preliminary considerations of the synthesis of ring C of cyathin A_3 led us to study the Diels-Alder reaction of substituted furans. We were particularly interested in the use of 2-methoxyfuran 1 as the diene. This interest stemmed from the fact that the adduct formed would already have two of the ring C oxygens in the proper position. Suitable elaboration of the six-membered ring thus obtained could give an appropriately substituted cycloheptenone.

In connection with another project the Diels-Alder reaction of 2-methoxyfuran with a number of dienophiles has been investigated by Dr. L. Browne in these laboratories[1]. It was found that the methoxyl substituent directs the mode of addition of the dienophile giving rise to the "ortho product" in accord with the numerous examples available[2] and with mechanistic considerations[3]. The furan has been previously prepared by other workers[4,5]. In these laboratories the compound is prepared by acid-catalyzed pyrolysis of commercially available 2,5-dihydro-2,5-dimethoxyfuran[1].

Treatment of 2-methoxyfuran with α-acetoxyacrylonitrile and with α-chloroacrylonitrile produced 6-acetoxy-6-cyano-1-methoxy-7-oxabicyclo[2.2.1]hept-2-ene 2 and

6-chloro-6-cyano-1-methoxy-7-oxabicyclo[2.2.1]hept-2-ene 3 respectively. We intended to reduce the cyano group to the corresponding primary amine which in turn could be transformed into a suitable leaving group. Elimination with ring expansion should furnish the desired ketone.



Both adducts were found to be thermally unstable, on standing at room temperature they resinify. In order to partially overcome this instability problem, they were hydrogenated to the corresponding 7-oxabicyclo[2.2.1]heptanes. It was anticipated that once the conditions for ring expansion had been established in the hydrogenated compounds, they might be applicable to 2 and 3.

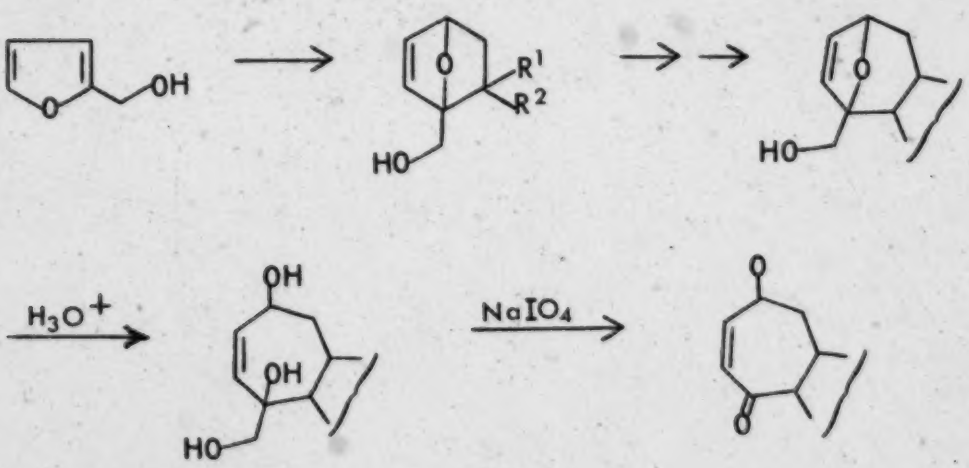
Attempts were made to reduce the cyano group by treatment with lithium aluminum hydride in ether[4,5]. Under these conditions, however, the adducts decomposed giving

rise to mixtures. These mixtures were found not to contain bicyclic materials since their nmr spectra lacked the signal for the bridgehead proton. The use of diborane[6] and disiamylborane[7] for the reduction of nitriles has been reported. In our hands diborane also led to decomposition of the adducts. Possibly the Lewis-acid character of the reagent cleaves the sensitive ketal bridge of our adducts.

Catalytic hydrogenation of the cyano group was not successful under the conditions investigated. Thus after hydrogenation of 2 or 3 in ether or ethyl acetate over palladized charcoal at 3 atmospheres for up to 48 hours, the starting material was recovered unchanged. The use of platinum oxide under similar conditions was found to cause extensive decomposition. The use of the latter catalyst in ammoniacal ethanol afforded starting material only.

The catalytic hydrogenation of nitriles under mild conditions using a rhodium catalyst has been reported by Freifelder[8]. The reductions are reported to take place at low pressure (2-3 atmospheres) using rhodium on alumina as the catalyst in ethanolic ammonia. Under these conditions no reduction of 3 could be detected. Treatment of 3 at 100 atmospheres in saturated ammoniacal methanol using rhodium on alumina as the catalyst, afforded a mixture of compounds. No bicyclic material could be detected by nmr. The only crystalline material isolated proved to be ammonium chloride.

At this point we decided to prepare a Diels-Alder adduct which did not contain the acid sensitive internal ketal. The adduct should be so constituted as to allow eventual conversion to the required ketone. Furfuryl alcohol was chosen as a substrate. After ring expansion and further transformations had been completed, acid treatment would hydrolyze the oxygen bridge leading to a 1,2-diol. The cleavage of the diol with periodic acid or lead tetraacetate[9] should produce the desired ketone function.



Alkylfurans, however, undergo Diels-Alder reactions satisfactorily only with reactive dienophiles such as maleic anhydride, maleimide, acetylene dicarboxylic esters, etc. It has been reported that acrolein and 2-methylfuran undergo a Diels-Alder reaction[10] when heated in an autoclave. Our attempts of achieving the addition of acrolein to furfuryl alcohol under those conditions resulted only in pyrolysis of the materials. At lower temperatures (refluxing benzene)

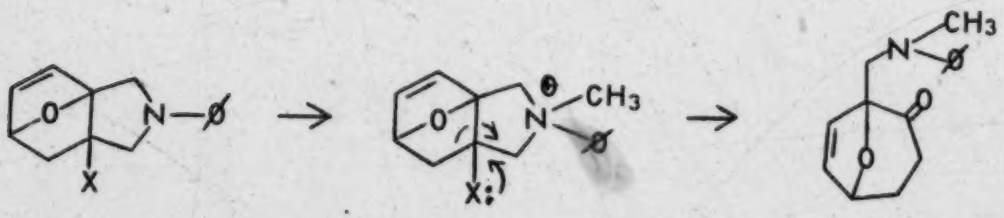
polymerization of the acrolein seemed to be the predominant reaction, the furfuryl alcohol was unreacted (by nmr). Lewis-acid catalyzed addition of dienophiles to furans and pyrroles has been reported[11]. The intermediate adducts are not isolated, instead their rearrangement products phenols and anilines are isolated in yields ranging from 45 - 55%. In our hands treatment of furfuryl alcohol with either acrolein or ethyl acrylate and boron trifluoride etherate led to polymerization. The use of copper fluoroborate as the catalyst afforded no reaction.

At this stage our attention was drawn to interesting internal Diels-Alder reaction with a furan ring acting as the diene. Bilovic, Stojanac and Hahn[12] reported that some allylarylfurfurylamines on standing at room temperature spontaneously isomerized to N-aryl-5,7a-epoxytetrahydroisoindolines.

4 R = H, CH_3, OCH_3 5

Seemingly, the allylic double bond is so situated as to facilitate the process to such an extent that such a poor dienophile as an isolated double bond would undergo a Diels-Alder addition. We felt that such compounds could be used for the synthesis of a cycloheptenone. Thus if a

suitably substituted allylamine could be prepared, it should undergo internal Diels-Alder reaction. After quaternization of the isoindoline, the salt should be prone to fragmentation leading to ring enlargement as shown below.

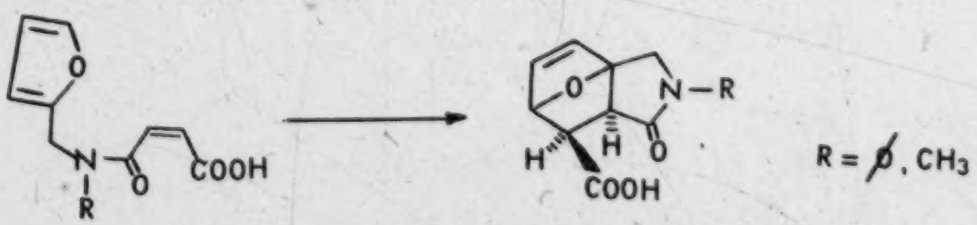


The preparation of compounds such as 5 was undertaken. The previous workers prepared the compounds by treatment of the corresponding N-arylfurfurylamines with allyl iodide. The resulting hydroiodides were treated with base to liberate 4. We could not, however, obtain crystalline hydroiodides and a modified approach was used. By treatment of N-phenylfurfurylamine with sodium hydride in DME followed by addition of allyl iodide, a 27% yield of 4 (R=H) was obtained. A better method for its preparation consisted of heating to reflux an equimolar mixture of N-phenylfurfurylamine and 2,6-lutidine with an excess of allyl bromide in acetone (75% yield). This method was reported to be useful for the preparation of quaternary ammonium salts[13]. In our hands, only the tertiary amine could be isolated.

While 4 (R=H) isommerized on standing to the internal Diels-Alder adduct 5 (R=H), all of our attempts to quaternize 5 were unsuccessful. At this stage, we felt that the quaternization had not taken place at least in part as a result of the low basicity of the anilino nitrogen. We therefore undertook the preparation of some alkylallylfurfurylamines.

These compounds should cyclize to the internal Diels-Alder adducts and these in turn should quaternize. If this were the case our original plans for ring enlargement could be investigated.

As a result we undertook a more general study of the intramolecular Diels-Alder cyclization of N,N-disubstituted furfurylamines. Further studies have been reported by Bilovic[14]. He found that on reaction of N-phenylfurfurylamine with maleic anhydride, the intermediate N,N-phenylfurfurylmaleamic acid 7 isomerized to 2-phenyl-3-oxo-5,7a-epoxy-3a,4,5,7a-tetrahydro-4-isoindoline carboxylic acid 8. The same reaction took place using N-methylfurfurylamine.



7 8

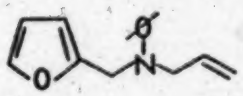
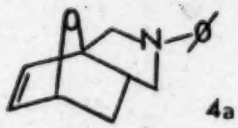
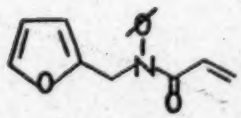
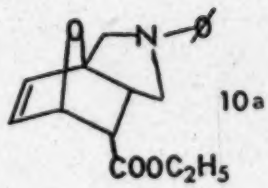
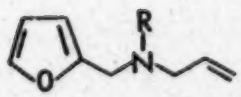
Our results are summarized on Table 1. The study was also extended to include oxygen instead of nitrogen as

the heteroatom linking diene and dienophile. These results are summarized on Table 2.

For comparison with 4 and 7, N-phenyl-N-furfuryl-acrylamide 9 and ethyl 4-(N-phenylfurfurylamino)crotonate 10 were prepared. The acrylamide 9 does not undergo the internal Diels-Alder reaction. On the other hand, 10 undergoes the cycloaddition to give 10a rapidly since we could not isolate it in the open form. These results may be explained by taking two factors into consideration: changes in dienophilicity through polarization of the double bond and steric requirements. The amide linkage, while polarizing the double bond, has sp^2 hybridization which causes the substituents to lie in the same plane. Models indicate that the C=C double bond cannot approach the ring as easily in the case of 9 as in 4. In the case of the maleamic acid 7, the carboxyl substituent on the double bond must increase its dienophilicity to such an extent that this overrides the steric factor.

In our initial efforts to obtain an N-substituted N-allylfurfurylamine with a substituent other than a phenyl group, N-allylfurfurylamine 11 and N-ethyl-N-allylfurfurylamine 12 were synthesized. These compounds failed to undergo cycloaddition at a variety of temperatures (room temperature to 105°). At the time we felt that a possible reason these compounds behaved differently from the N-phenyl analog was due to the different steric effects of the substituents.

TABLE 1

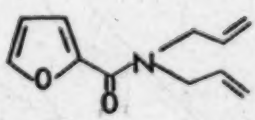
Compound	Structure	
4		 4a
9		N.R.
10		 10a
		N.R.

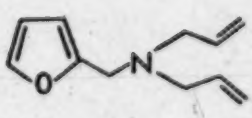
11 R = H

12 R = Et

13 R = t-Bu

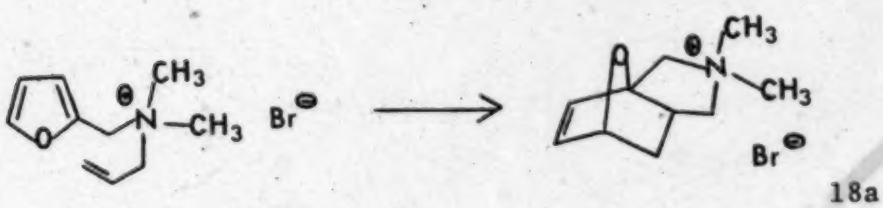
14 R = Ac

15  N.R.

16  N.R.

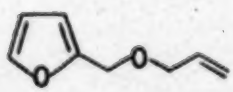
17

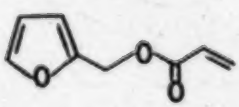
17a

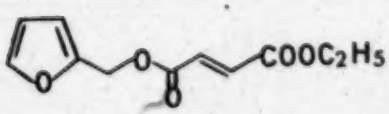
18 

18a

TABLE 2

19  N.R.

20  N.R.

21  N.R.

22

22a

Thus, if the phenyl and furan rings, for steric reasons, are well separated, the allyl substituent is in a favourable position to undergo the Diels-Alder reaction. To test this assumption N-tert-butyl-N-allylfurfurylamine 13 was prepared. This material, however, does not cyclize.

We next investigated whether the difference between the alkyl substituted amines and 4 was electronic in nature. It may be postulated that the phenyl ring through delocalization of the nitrogen lone pair polarizes the allylic double bond or distorts the tetragonal geometry of the nitrogen in such a way as to render the cycloaddition reaction less difficult. In order to study this we prepared N-allyl-N-furfuryl-acetamide 14. This amide does not cyclize, likely because the change from tetragonal to trigonal geometry of the nitrogen precludes the effective interaction of the allyl groups and the furan ring.

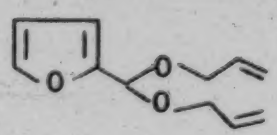
Another possible way of weighing the role of the polarization of the allylic double bond is to form a quaternary ammonium salt. The positive charge on the nitrogen should enhance the polarization of the double bond. To this end, N,N-dimethyl-N-allylfurfurylammonium bromide 18 was prepared. The salt was isolated as a thick oil that could not be made to crystallize. Its nmr shows: δ 3.31 (s, 6H, CH_3NCH_3), 4.35 (d, J=6Hz, 2H, $NCH_2CH{=}CH_2$), 5.06 (s, 2H, CH_2N), 5.58 - 6.14 (m, 3H, $CH{=}CH_2$), 6.47 (d of d,

J=3Hz, J=1.5Hz, 1H, furan C4 proton), 7.01 (d, J=3Hz, 1H, furan C3 proton), 7.58 (d, J=1.5Hz, 1H, furan C5 proton) which is consistent with the open form. Bilovic has reported that 5 can be converted to its retro Diels-Alder product 4 by heating it above its melting point for a short time. We felt that if the same was true for the conversion of 18a to 18 and that if this is taking place even at room temperature, we might be able to observe the Diels-Alder reaction at lower temperatures. However, when nmr spectra were recorded at temperatures of -50° and -95°, no evidence of cycloaddition could be detected.

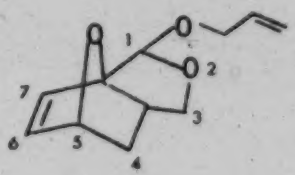
Two months later it was observed that the previously liquid 18 had solidified. Investigation of this material showed no evidence for the furan ring and indications were that complete conversion to the internal Diels-Alder adduct 18a had taken place. Thus the nmr of this material shows two vinyl protons as a doublet at δ 6.67 (J=6Hz) and as a doublet of doublets at δ 6.45 (J=6Hz, J=2Hz). The bridgehead proton can be observed at δ 5.16 as a doublet of doublets (J=4Hz, J=2Hz). The methyl signals are no longer equivalent, instead two sharp singlets at δ 3.6 and δ 3.74 are evident in agreement with the cyclic structure where the methyl groups are in different chemical environments. The coupling constants observed for the vinyl and bridgehead protons are in close agreement with those reported by Browne[1] and Gagnaire and Payo-Subiza[15] for some 7-oxanorbornene derivatives.

Concurrent with the preparation of the aforementioned compounds, the synthesis of systems having an oxygen instead of nitrogen between the furan and double bond was undertaken. It was found that allyl furfuryl ether 19, furfuryl acrylate 20 and ethyl furfuryl fumarate 21 do not give rise to the corresponding internal adducts. That 20 does not form a cycloadduct is in line with the failure of N-allyl-N-furfurylacrylamide 9 to undergo cycloaddition. On the other hand the failure of 19 and 21 to cyclize further implicates a special effect of the phenyl substituent in the nitrogen series.

The diallyl acetal of furfuraldehyde 22 was prepared by heating to reflux a 5:1 mixture of allyl alcohol and furfuraldehyde in benzene containing p-TSA with azeotropic removal of water. After distillation of the reaction products a 1:1 mixture of 22 with the cyclized material 22a was obtained. The ratio of 22 to 22a was determined by integration of the furan C5 proton and one of the protons at C4 of the adduct.



22



22a

Examination of the nmr of the mixture of 22 and 22a after two months did not show any appreciable change. However, 14 months later complete conversion to 22a had taken place as indicated by nmr. A complete analysis of the spectra is possible (see Experimental) and agrees with the proposed structure. It was subsequently found that conversion of the mixture to 22a can be accomplished by heating to reflux in benzene for 72 hours. Higher temperatures lead to reversal of the addition. Thus when 22a was heated at 140° for three hours, a 2:3 mixture of 22 and 22a was obtained.

To assess the influence of two substituents in the ease of cycloaddition, N,N-diallylfurfurylamine 16 was prepared via N,N-diallylfuramide 15. Neither 15 nor 16 could be induced to form the internal Diels-Alder product. The lack of cyclization of 15 can again be explained in terms of the geometry imposed by the amide bond. The fact that 16 does not cyclize even after prolonged heating in refluxing benzene whereas 22 does, may be due to the greater degree of flexibility in the acetal vs the amine.

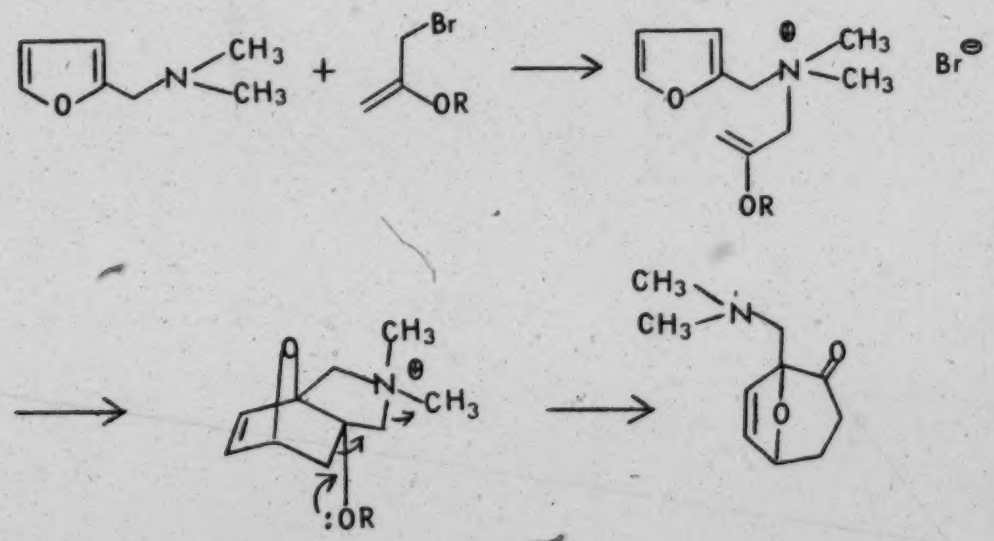
While 16 does not cyclize, cyclization does proceed readily after quaternization to triallylfurfurylammonium bromide 17. By treatment of 16 with allyl bromide, the salt 17 can be obtained in crystalline form. When it is dissolved in minimum amounts of methanol, 17a is formed within 48 hours.

This cyclization is more rapid than that of 18, presumably because of the greater probability of attaining the proper conformation for bond formation.

It is evident from the results obtained that the ease of cyclization is increased with increasing dienophilic character of the double bond, an observation generally encountered in Diels-Alder reactions[2,3]. It is difficult with the available information to generalize on the factors governing these internal Diels-Alder reactions. It can be seen that the geometry of the addends plays an important part. However, the role of the substituents on the nitrogen atom is hard to assess. It could be said that the phenyl interacts with the lone pair of the nitrogen effectively diminishing the rate of inversion at this centre. This in turn would permit a better interaction of diene and dienophile allowing reaction to occur. Polarization of the double bond as a consequence of polarization of the nitrogen may be an important factor. Both explanations are in agreement with the results obtained with the quaternary salts. It can however be argued that a conclusion should not be drawn since in the salts the nitrogen is fully substituted and the steric factor may now be the controlling factor. It is clear that further work will be necessary before a complete definition of the scope of this reaction can be given.

Regardless of the theoretical implications, the

ease of preparation of 17a, 18a and 22a suggest that compounds of this type are possible intermediates in a ring enlargement sequence as discussed initially and as hypothesized below.



EXPERIMENTAL

Melting points were determined on a Fischer-Johns or Leitz-Wetzlar hot-stage melting point apparatus and are uncorrected.

Microanalyses were performed by the Microanalytical Laboratory of this department.

Infrared spectra were recorded on a Perkin-Elmer Model 337 grating infrared spectrophotometer, a Unicam SP1000 grating infrared spectrophotometer, or a Perkin-Elmer Model 421 dual grating infrared spectrophotometer.

Nuclear magnetic resonance spectra were measured using a Varian Associates Model A-60 spectrometer or a Varian Model HR-100 spectrometer with tetramethylsilane as internal standard. Deuterium exchangeable protons are noted in text as D_2O.

Mass spectra were recorded on an A.E.I. Model MS-9 mass spectrometer or an A.E.I. Model GC/MS mass spectrometer with a WB separator.

Chemical ionization spectra were recorded on an A.E.I. Model MS-12 mass spectrometer with a chemical ionization source and ammonia as internal standard.

N-Phenyl-5,7a-epoxy-3a,4,5,7a-tetrahydroisoindoline 4a

Freshly distilled N-phenylfurfurylamine[12] (3.62 g, 20 mmoles) and 2,6-lutidine (2.4 g, 22.4 mmoles) was dissolved in dry acetone (50 ml). Allyl bromide (4.97 g, 41 mmoles) was added to the solution and the mixture was refluxed under nitrogen for three hours. After the addition of more allyl bromide (15.7 mmoles), refluxing was continued for 11 hours. The solution was filtered and the filtrate was triturated with ether to remove further 2,6-lutidine hydrobromide formed. The solvent and excess allyl bromide were removed under vacuum leaving an orange oil. After three days a dark semi-solid had formed. After recrystallization from ethanol 3.2 g (75% yield) of 4a was obtained. mp 119 - 120°. (lit.[12] 120 - 121°). The spectral data is consistent with that reported.

The isoindoline 4a was also prepared as described below.

Sodium hydride (1.35 g, 57% oil dispersion) was added to a solution of N-phenylfurfurylamine[12] (5 g) in dry dimethoxyethane (100 ml). The slurry was refluxed under nitrogen for 30 minutes. Allyl iodide (4.87 g, 29 mmoles) was added and the mixture refluxed for 18 hours.

Water was added to the cool solution (100 ml); the aqueous layer was extracted with CH_2Cl_2 (3 x 100 ml). The dark red oil obtained after evaporation of the dried solvent (Na_2SO_4), was chromatographed on alumina (100 g). After elution with pentane (300 ml), the column was eluted with CH_2Cl_2 to give a brown oil. The oil solidified on standing (two days) and the solid was recrystallized from 98% EtOH. A 27.5% (1.7 g) yield of 4a was thus obtained.

N-furfuryl-N-phenylacrylamide 9

To a mixture of N-phenylfurfurylamine (1.1 g) and 1N sodium hydroxide (8 ml), acryloyl chloride (1.81 g) was added in one portion with vigorous stirring. Fifteen minutes later the mixture was diluted with ether (30 ml) and water (10 ml). The layers were separated and the aqueous layer extracted with ether (10 ml). The ethereal layer and extract were combined and washed (dilute HCl, saturated $NaHCO_3$). Evaporation of the dried ($MgSO_4$) solvent left the crude acrylamide as a reddish oil (1.345 g). Percolation through alumina gave 9 as a yellow liquid n_D^{20} 1.5852

ir (liquid film): 1670 cm^{-1} (amide).

nmr: δ 5.04 (s, 2, $C\underline{H}_2N$).

mass spectrum: m/e 227(55), 213(32), 146(34), 106(19), 104(20), 93(13), 81(100), 77(34), 55(35), 53(26), 51(17).

Anal. Calcd. for $C_{14}H_{13}NO$: C, 73.99; H, 5.77; N, 6.16.

Found: C, 73.74; H, 5.77, N, 6.16.

N-Phenyl-4-(endo-ethoxycarbonyl)-5,7a-epoxy-3a,4,5,7a-tetrahydroisoindoline 10a.

A mixture of N-phenylfurfurylamine (2 g), 2,6-lutidine (1.24 g) and ethyl 4-bromocrotonate (2.5 g) was refluxed under nitrogen for 36 hours in dry acetone (50 ml). Most of the solvent was removed under vacuum and the solution was triturated with ether to remove 2,6-lutidine hydrobromide. The filtrate was concentrated and triturated with pentane. The solid that separated was recrystallized from Skellysolve B-Et_2O to obtain 10a as a white fiber-like material (1.48 g). mp 91.5 - 92.5°.

ir$_{(CHCl_3)}$: 1735 (ester), 1600 cm^{-1} (aromatic).

nmr: δ 7.42 - 6.47 (m, 6, H 7 and phenyl protons), 6.37 (d of d, 1, J=6, 1.5 Hz, H 6), 5.28 (d of d, 1, J=4.5, 1.5 Hz, H 5), 4.13 (q, 2, J=7Hz, $COOCH_2CH_2$), 1.26 (t, 3, J=7Hz, $COOCH_2CH_3$).

mass spectrum: m/e 285(6), 204(7), 130(8), 104(6), 82(6), 81(100), 77(15), 53(21), 51(7).

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.47; H, 6.85; N, 4.70.

N-Allylfurfurylamine 11

Furfuraldehyde (19.2 g) was added with stirring to cool (ice-water bath) allylamine (13.7 g). After addition was completed (10 minutes) the mixture was stirred at room

temperature for one hour. Powdered sodium hydroxide (2 g) was added to the reaction mixture with stirring. The layers were separated after ten minutes and the organic layer dissolved in ether (50 ml). The ethereal solution was dried (brine, Na_2SO_4) and the solvent removed. The residue was distilled at reduced pressure to obtain N-allylfurfurylimine as a colourless liquid (24 g, 85%) bp 74 - 75°/10 mm. To a cool solution (ice-water bath) of the imine, under nitrogen, lithium aluminum hydride was added in one portion (7.6 g). After two hours the cooling bath was withdrawn and the mixture was left at room temperature for 12 hours. The reaction mixture was worked-up by successive addition of water (7 ml), 15% aqueous sodium hydroxide solution (10 ml) and water. The slurry was filtered and the residue left after evaporation of the solvent was distilled at reduced pressure. N-allylfurfurylamine 11 was obtained as a colourless liquid (11.3 g, 42%). bp 65 - 68°/9 mm n_D^{20} 1.4869.

ir (liquid film): 1650 (C=C), 1605 cm^{-1} (aromatic).

nmr: δ 7.35 (m, 1, furan C4 H), 6.38 - 6.1 (m, 2, furan C2 and C3 H's), 6.1 - 5.6 (m, 1, $C\underline{H}=CH_2$), 5.4 - 4.97 (m, 2, $CH=C\underline{H}_2$), 3.78 (s, 2, $ArC\underline{H}_2N$), 3.35 - 3.16 (m, 2, $C\underline{H}_2CH=CH_2$).

mass spectrum: m/e 137(9), 108(19), 81(100), 68(19), 56(17), 53(47), 41(42).

Anal. Calcd. for $C_8H_{11}NO$: C, 70.08; H, 8.08; N, 10.21.
Found: C, 70.34; H, 8.20, N, 10.32.

N-Allyl-N-ethylfurfurylamine 12

N-Acetyl-N-allylfurfurylamine (1 g) was reduced with lithium aluminum hydride in ether in the usual manner (see preparation of 11) to give a quantitative yield of crude 12 An analytical sample was obtained by bulb to bulb distillation 60°/0.5 mm n_D^{20} 1.4740.

ir (liquid film): 3055 (C=C), 1645 (C=C), 1595 cm^{-1} (aromatic).

nmr: δ 7.34 (m, 1, furan C5 H), 6.34 - 6.16 (m, 2, furan C4 and C3 H's), 6.14 - 5.56 (m, 1, $C\underline{H}=CH_2$), 5.37 - 4.96 (m, 2, $CH=C\underline{H}_2$), 3.63 (s, 2, $Ar\underline{CH}_2$), 3.2 - 3.0 (m, 2, $\underline{CH}_2CH=CH_2$), 2.52 (q, 2, J=7Hz, $\underline{CH}_2CH_3$), 1.05 (t, 3, J=7Hz, $CH_2\underline{CH}_3$).

mass spectrum: m/e 165(7), 150(11), 81(100), 57(24), 41(18).

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.88; H, 9.31; N, 8.43.

N-tert-Butylfurfurylamine

tert-Butylamine (0.4 moles) was added to a solution of furfuraldehyde (0.2 moles) in benzene (100 ml). After 12 hours at room temperature the excess amine and benzene were evaporated under vacuum. The residue was dissolved in ether (300 ml) and cooled (ice-water bath). To the cooled solution lithium aluminum hydride (0.1 moles) was added in

one portion under nitrogen. The slurry was vigorously stirred at room temperature for 12 hours. Work up in the conventional manner gave a 95% yield of the crude amine. Distillation at reduced pressure gave N-tert-butylamine as a colourless liquid. (84% yield) bp 66°/14 mm n_D^{20} 1.5031.

ir (liquid film): 1600 (aromatic), 1210 cm^{-1} (t-Bu).

nmr: δ 7.34 (m, 1, furan C5 H), 6.38 - 6.1 (m, 2, furan C3 and C4 H's), 3.76 (s, 2, CH_2N), 1.17 (s, 9, t-Bu).

mass spectrum: m/e 153(2), 138(17), 81(100), 53(20), 42(14), 41(16).

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.89; N, 9.14.
Found: C, 70.90; H, 9.87; N, 9.14.

N-Allyl-N-tert-butylfurfurylamine 13

To N-tert-butylfurfurylamine (3.37 g) in ether (80 ml) at -50°, an n-butyllithium solution (1.275N, 20 ml) was added slowly with stirring under nitrogen (10 minutes). Allyl bromide (2.9 g) in ether (10 ml) was then added over 10 minutes. The solution was left at room temperature for 14 hours. Water was added (1 ml) followed by magnesium sulphate. After removal of drying agent and solvent the residue was distilled at reduced pressure. The allylamine 13 was collected at 48°/0.4 mm (1.4 g) n_D^{20} 1.4716.

ir: 1650 (C=C), 1600 cm^{-1} (aromatic).

nmr: δ 7.31 (m, 1, furan C5 H), 6.38 - 6.05 (m, 2, furan C4 and C3 H's), 4.03 - 5.48 (m, 1, $CH=CH_2$), 5.28 - 4.74 (m, 2,

$\underline{CH}=C\underline{H}_2$), 3.72 (s, 2, $Ar\underline{CH}_2$), 3.37 - 3.14 (m, 2, $\underline{CH}_2CH=CH_2$).

mass spectrum: m/e 193 (2), 178(21), 81(100), 57(7), 53(16), 41(23).

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25.

Found: C, 74.83; H, 10.30; N, 7.47.

N-Acetyl-N-allylfurfurylamine 14

N-Allylfurfurylamine (3.3 g) was added to a mixture of acetic anhydride (10 ml) and pyridine (20 ml) in dry CH_2Cl_2 (100 ml). After 18 hours the solvent was distilled under vacuum. The residue was dissolved in ether (150 ml) and washed with ice-cold dilute HCl (2 x 20 ml), saturated $NaHCO_3$ and brine. The dried ($MgSO_4$) solvent was evaporated leaving the title compound as a yellow oil (3.15 g, 73%). An analytical sample was secured by bulb to bulb distillation bp 190°/0.3 mm n_D^{20} 1.5031.

ir (liquid film): 1655 cm^{-1} (amide).

nmr: δ 7.34 and 6.26 (two m, 1 and 2 respectively, furan protons), 6.14 - 4.9 (m, 3, $\underline{CH}=C\underline{H}_2$), 4.55 and 4.4 (two s, 2, furan benzylic protons), 4.08 - 3.8 (m, 2, $\underline{CH}_2CH=CH_2$), 2.11 and 2.09 (two s, 3, $NCOC\underline{H}_3$).

mass spectrum; m/e 179(7), 138(29), 96(100), 81(65), 56(19), 53(37), 43(61), 41(29), 39(24).

Anal. Calcd. for $C_{10}H_{13}NO$: C, 67.02; H, 7.31; N, 7.82.

Found: C, 67.21; H, 7.49; N, 7.97.

N,N-Diallyfuramide 15

To a solution of furoyl chloride (13.05 g, 0.1 moles) in ether (200 ml), a mixture of diallylamine (9.7 g, 0.1 moles) and triethylamine (0.11 moles) in ether (100 ml) was added dropwise (30 minutes) with external cooling (ice-water bath). The vigorously stirred slurry was left for three hours at room temperature. To the reaction mixture, ether (100 ml) and water (40 ml) were added and the layers separated. The ethereal layer was dried (brine, $MgSO_4$) and the solvent was evaporated. Distillation at reduced pressure afforded the amide as a slightly yellow liquid (16.1 g, 84%)
bp 105 - 108°/0.5 mm n_D^{20} 1.5247.
ir (liquid film): 1630 cm^{-1} (amide).
nmr: δ 7.5, 7.05 and 6.47 (3m, 3, furan H), 6.3 - 5.0 (m, 6, 2 $CH{=}CH_2$), 4.14 (m, 4, 2 $CH_2C{=}C$).
mass spectrum: m/e 191(13), 150(8), 108(6), 96(7), 95(100), 94(20), 70(11), 41(21).
Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32.
Found: C, 68.85; H, 6.95; N, 7.09.

N,N-Diallylfurfurylamine 16

Lithium aluminum hydride in ether (20 ml, 1M) was added dropwise, with stirring, under nitrogen, to a solution of N,N-diallylfurfurylamide (1.97 g) in ether (30 ml). After addition (20 minutes), the solution was left for five

hours at room temperature. It was worked up as in previous similar reactions to obtain N,N-diallylfurfurylamine as a colourless liquid (1.692 g, 96%). Bulb to bulb distillation (170°/0.1 mm) provided an analytical sample n_D^{22} 1.4834.

ir (liquid film): 1645 cm^{-1} (C=C).

nmr: δ 7.40, 6.35 and 6.19 (3m, 3, furan protons), 6.1 - 5.0 (m, 6, 2 $C\underline{H}=C\underline{H}_2$), 3.65 (s, 2, $ArC\underline{H}_2N$), 3.1 (m, 4, 2 $C\underline{H}_2C=C$).

mass spectrum: m/e 179(23), 178(20), 177(26), 150(9), 136(10), 96(9), 81(100), 53(14), 41(22).

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.59; H, 8.53; N, 7.90.
Found: C, 74.39, 74.68; H, 8.74, 8.75; N, 7.92, 8.06.

Triallylfurfurylammonium bromide 17, N,N-diallyl-5,7a-epoxy 3a,4,5,7a -tetrahydroisoindolinium bromide 17a

An equimolar mixture (1 mmole) of N,N-diallylfurfurylamine and allyl bromide were mixed and left overnight. The crystals formed were washed with ether to obtain 17 in 78% yield mp 140 - 143°.

nmr: δ 4.92 (s, 2, $ArC\underline{H}_2$), 4.16 (d, 8, $NC\underline{H}_2$).

The salt 17 was dissolved in the minimum amount of methanol and the solvent allowed to evaporate at room temperature. After 48 hours a solid had formed. It was triturated with ether to obtain the cyclized salt 17a (89%) mp 149 - 150°.

nmr: δ 6.75 (d, 1, J=6Hz, H-7), 6.47 (d of d, 1, J=6, 1.5Hz, H-6).

Anal. Calcd. for $C_{10}H_{16}BrNO$: C, 48.82; H, 6.50; N, 5.69. Found: C, 48.66; H, 6.81; N, 5.41.

Dimethylallylfurfurylammonium bromide 18, N,N-dimethyl-5,7a-epoxy,3a,4,5,7a-tetrahydroisoindolinium bromide 18a

An excess of allyl bromide was added to N,N-dimethylfurfurylamine (1 g), dissolved in dry methanol (10 ml). After standing at room temperature for 90 minutes the solvent and excess allyl bromide were evaporated under vacuum. The ammonium salt 18 was obtained quantitatively as a yellow oil.

nmr: δ 7.58 (m, 1, furan C5 H), 7.01 (m, 1, furan C3 H), 6.48 (m, 1, furan C4 H), 6.14 - 5.58 (m, 3, $CH{=}CH_2$), 5.06 (s, 2, $ArCH_2$), 4.35 (d, 2, J=6Hz, $CH_2CH{=}CH_2$), 3.31 (s, 6, CH_3NCH_3).

After 60 days of standing at room temperature 18 is transformed to a solid corresponding to 18a. This material was recrystallized from EtOH-Et_2O. mp 185 - 186°.

nmr: δ 6.67 (d, 1, J=6Hz, C7 H), 6.44 (d of d, 1, J=6, 1.5Hz, C6, H), 5.16 (d of d, 1, J=4, 1.5Hz, C3 H), 4.8 (d, 1, J=13.5Hz, C1 H), 4.06 (d, 1, J=13.5Hz, C1 H), 4.72 - 4.05 (m, 1, C3-H), 3.78, 3.62 (two s, 6, 2 NCH_3), 1.53 (d of d, 1, J=7.5Hz, C4, Hendo).

Allyl furfuryl ether 19

The ether was prepared from furfuryl alcohol and allyl bromide in a conventional way. bp 167 - 168° n_D^{20} 1.4709 (lit.[16] bp 173.5 - 174.5° n_D^{20} 1.4718).

Furfuryl acrylate 20

The ester 20 was prepared by the method used in the preparation of 21. It was obtained as a colourless liquid (85%) bp 82 - 83°/10 mm (lit.[17] bp 93°/16 mm).

Furfuraldehyde diallyl acetal 22

A mixture of furfural (48 g, 0.5 moles), allyl alcohol (145 g, 2.5 moles) and p-TSA (50 mg) was dissolved in benzene (500 ml). The solution was heated to reflux with azeotropic removal of water for 20 hours. Triethylamine was added (1 ml) and solvent and excess allyl alcohol were evaporated under vacuum. The black residue was distilled at reduced pressure to obtain a 1:1 mixture of furfural diallyl acetal 22 and 1-allyloxy-5,7a-epoxy-1,3,3a,4,5,7a-hexahydroisobenzofuran 22a (52 g) bp 100 - 105°/6 mm.

nmr: δ 7.45 (m, 1, furan C4 proton), 3.62 (t, 1, J=8Hz, C4 H of adduct).

1-Allyloxy-5,7a-epoxy-1,3,3a,4,5,7a-hexahydroisobenzofuran 22a

One gram of the sample obtained in the above-mentioned experiment was refluxed in benzene (15 ml) for 72 hours. The solvent was distilled under vacuum to leave one gram of the cyclized material 22a. An analytical sample was prepared by bulb to bulb distillation 80°/0.1 mm n_D^{20} 1.4918
ir (liquid film): 3060 and 1650 cm^{-1} (C=C).
nmr: δ 6.5 (d, 1, J=6Hz, H 7), 6.32 (d of d, 1, J=6, 1.5 Hz, H-6), 6.2 - 5.72 (m, 1, $CHCH_2$), 5.42 - 5.0 (m, 3, $CH=CH_2$ and H 5), 5.18 (s, 1, OCHO), 4.27 (t, 1, J=8Hz, H 3), 4.4 - 3.56 (m, 2, $OCH_2CH=CH_2$), 3.56 (t, 1, J=8Hz, H 3), 2.28 (d of q, 1, J=8, 3Hz, H-3a), 1.62 (d of d of d, 1, J=12, 4, 3Hz, H-4x), 1.47 (d of d, 1, J=12, 8Hz, H 4n).
mass spectrum: m/e (M^+-57), 137(41), 123(15), 109(37), 108(82), 95(32), 81(28), 80(96), 79(40), 41(100).
Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.03; H, 7.15.

Ethyl furfuryl fumarate 21

To a solution of furfuryl alcohol (9.8 g) and triethylamine (11.1 g) in ether (200 ml) at -50°, trans-β-ethoxycarbonylacryloyl chloride (16.93 g) was added dropwise with stirring. The mixture was allowed to warm to room temperature after addition was completed (30 minutes) and stirred for 14 hours. Water (50 ml) was added and the

layers separated. The ethereal layer was washed (diluted HCl, saturated $NaHCO_3$) and dried (Na_2SO_4). The residue left after distillation of solvent was percolated through alumina (100 g) using CH_2Cl_2 as eluent. Ethyl furfuryl fumarate was obtained as a yellowish liquid (19.7 g, 87%). A pure sample was prepared by bulb to bulb distillation 180°/0.1 mm n_D^{20} 1.4910.

ir (liquid film): 1730 cm^{-1} (ester).

nmr: δ 7.43 (m, 1, furan C5 H), 6.86 (s, 2, HC=CH), 6.51 - 6.28 (m, 2, furan C4 and C3-H), 5.19 (s, 2, $ArCH_2$), 4.24 (q, 2, J=7Hz, $COOCH_2CH_3$), 1.29 (t, 3, J=7Hz, $COOCH_2CH_3$).

mass spectrum: m/e 224(7), 151(12), 128(31), 127(15), 100(14), 99(24), 97(30), 82(13), 81(100), 80(13), 69(10), 55(18), 54(15), 53(45), 52(44), 51(11), 43(11), 41(29), 39(27).

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 59.07; H, 5.47.

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